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α-ACYLIMINIUM ION-ACETYLENE CYCLISATIONS†

H. E. SCHOEMAKER,[1] TJ. BOER-TERPSTRA, J. DIJKINK and W. N. SPECKAMP*
Laboratory for Organic Chemistry, University of Amsterdam, P.O. Box 20241, 1000 HE Amsterdam, The Netherlands

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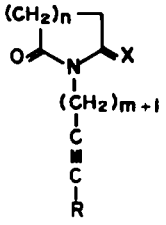
Abstract—Cyclisation of acetylenic ethoxylactams **1b–12b** leads to bridgehead nitrogen bicyclic ketones in excellent yields. The reaction is weakly acid-catalysed and proceeds at ambient temperature. The observed regioselectivity effect is discussed in terms of stability of *exo* vs *endo* vinyl cations and ring strain effects. The high yield conversion of N-(5-hexynyl)-ethoxy lactams **7b** and **8b** in the 5/8 and 6/8 fused bicyclic ketolactams **7c** and **8c** deserves special attention.

Cationic π-cyclisation of α-acyliminium ions has been developed into a general method[2] for the stereoselective synthesis of heterocyclic compounds. The synthetic potential of the latter technique can be enhanced considerably through the study of two of the most important aspects of this reaction, viz. the search for novel initiating systems[3] and the introduction of different functional groups suitable as participating π-moieties in these cyclisations. In the latter context the behaviour of the acetylene bond as the π-moiety in the cyclisation reaction was investigated.

Starting materials. As model compounds the N-substituted ω-ethoxylactams **1b–12b** were selected in which both the effects of ringsize and terminal acetylene substituents could be investigated. The ethoxy-lactams can be obtained by $NaBH_4/H^+$ reduction of the corresponding imides **1a–12a**. All of the imides used were synthesised according to the oxidation–reduction technique[4] in which the N–H imide is condensed at room temperature with the appropriate alcohol in presence of triphenylphosphine and dimethylazodicarboxylate.



n = 1	n = 2	R	m	n = 1	n = 2
X=O				X=C(H)OEt	
1a	**2a**	H	O	**1b**	**2b**
3a	**4a**	H	1	**3b**	**4b**
5a	**6a**	H	2	**5b**	**6b**
7a	**8a**	H	3	**7b**	**8b**
9a	**10a**	Me	1	**9b**	**10b**
11a	**12a**	Me	2	**11b**	**12b**

Fig. 1.

Cyclisations. The cyclisation experiments were carried out with chromatographically homogeneous samples. Although the actual starting material in this type of ring closure is the ethoxylactam, the real intermediate most probably is the cyclic α-acyliminium species[5] A.

Cyclisation of **3b** in HCOOH for 72 hr at room temperature afforded after hydrolysis of the intermediate vinylformate ester and work-up the bicyclic ketone **3c** in 97% yield as an oil, which crystallised upon standing. Compound **3c** was hydrogenated (H_2, PtO_2, AcOH) to a mixture of compounds **13a** and **13b**. From this mixture the known[6] lactam alcohol **13a** crystallised.

The cyclisation reaction of **4b** had to be performed in a more dilute solution to avoid the formation of the dimeric product C. Due to the rather slow cyclisation rate of the α-acyliminium ion-acetylene cyclisations compared to the corresponding olefin cyclisations, the acid-catalysed dimerisation reaction[7] via the enamide B begins to compete. Formation of the enamide B in the glutarimide series is a fast (and reversible) process, while in general the 5-membered ethoxylactams are less prone to enamide formation. Thus, cyclisation of 0.5 mmole of **4b** in 3 ml of HCOOH afforded a 5:1 mixture of **4c** and the dimer C (R_1 = 3-butynyl, n = 2) while cyclisation of 0.5 mmole of **4b** in 40 ml of HCOOH (72 hr, room temp.) afforded after work up exclusively the bicyclic ketone **4c** in 88% yield.

In general, purification of the reaction products via column chromatography or distillation is not possible due to severe decomposition. Thus, in an attempt to separate **4c** and the dimer C (*vide supra*) via column chromatography only dimer C[8] was isolated in 12% yield and compound **4c** had decomposed completely.

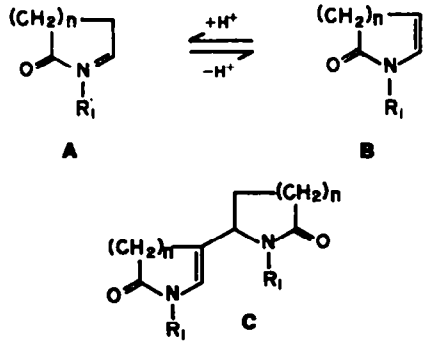


Fig. 2.

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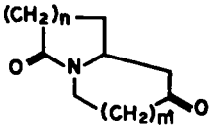
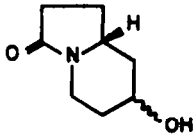
Enamide formation was the sole reaction observed in the HCOOH- experiments with compound **2b**. No trace of cyclised products could be detected. Treatment of compound **1b** with HCOOH resulted only in the recovery of starting material.

Although according to the Baldwin classification[9] a 5-*endo*-Dig ring closure is termed as a favored process, the formation of the relatively strained 6/5 and 5/5 fused bicyclic ketones is rather difficult in this type of α-acyliminium ion cyclisations with unactivated acetylenes.



3c: n = 1, m = 1
4c: n = 2, m = 1
5c: n = 1, m = 2
6c: n = 2, m = 2
7c: n = 1, m = 3
8c: n = 2, m = 3



13a: —OH
13b: —OH

Fig. 3.

Aiming at the improvement of synthetic routes towards 7- and higher membered rings, the ring closure of alkyne homologs was also investigated. Thus, cyclisation of **5b** and **6b** in HCOOH (5 days, room temp., 0.013 mole/l) afforded the crystalline 5/7 and 6/7 fused bicyclic ketones **5c** and **6c** in 92% resp. 88% yield. The latter results were somewhat surprising in view of the rather sluggish cyclisation reactions of the corresponding olefinic ethoxylactams.[10] The attractive yield of the alkyne reactions prompted us to study the cyclisation—inducing 8-membered ring formation—of the 5-hexynyl substituted ethoxylactams.

Cyclisation of **8b** in HCOOH afforded after 6 days a mixture of enamide B (R_1 = 5-hexynyl, n = 2) ethoxylactam **8b** and cyclised product **8c**. When the mixture was stirred over a period of 14 days, the sole product obtained (75% yield) after aqueous work-up, was the crystalline 6/8 fused bicyclic ketone **8c**. In a similar manner **7b** afforded the crystalline 5/8 fused bicyclic ketone **7c** in 80% yield.

The structure of the above mentioned products **3c–8c** was evident from the ^{1}H NMR analysis, important characteristics being the broad signal varying from δ = 3.40–3.80 for the axial tertiary N–CH proton and the multiplet varying from δ = 3.80–4.90, for the deshielded secondary N–CH proton due to the anisotropic effect of the amide carbonyl. In the 8-membered ring ketones the pseudo axial secondary N–CH proton is observed separately as a triplet (J = 11 Hz) at δ = 2.91 in compound **7c** and δ = 3.13 in compound **8c**. The abovementioned results clearly indicate the terminal alkyne C atom as the most reactive centre, most likely as a result of the marked difference in stability of primary vs secondary vinyl cations.

In the case of a methylsubstituted acetylene, the π-moiety is electronically unbiased, so *a priori* both reaction products may be expected. Recent results[11] on the hydrolysis of vinyltriflates indicate that bent vinyl cations are less stable than linear vinyl cations. Also the formation of the 5-membered D-ring in biomimetic steroid synthesis[12] involving acetylene participation indicates a preference for the formation of a cyclisation product via a linear vinyl cation.[13]

Cyclisation of the C–Me substituted alkyne **10b** (HCOOH, room temp., 3 days) afforded a mixture of two cyclised compounds **10c** and **10d** (combined yield 92%) in a ratio of approximately 5:1 (based upon NMR analysis). As expected 5-membered ring formation via a linear vinyl cation is the preferred mode of cyclisation.

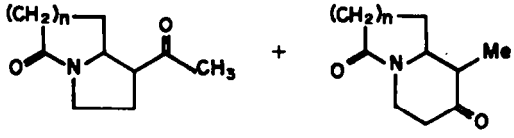
Cyclisation of **9b** (HCOOH, room temp., 3 days) also afforded a mixture of two compounds **9c** and **9d** (combined yield 91%), however, the ratio **9c**:**9d** being 1:9. Compound **9d** crystallised from the product mixture. Thus, in the latter addition of the alkyne 6-membered ring formation is the preferred reaction mode. The foregoing results most probably reflect the difference in ring strain of the corresponding N-bridgehead azabicyclics.

In the ^{1}H NMR spectrum of compound **9d** the characteristic signals for the axial tertiary N–CH proton and the deshielded secondary N–CH proton were immediately apparent. The (pseudo) equatorial position of the Me substituent was evident from the width of the tertiary N–CH signal possessing a large axial–axial coupling with the CHMe proton.

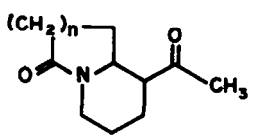
Severe decomposition during column chromatography or distillation prevented the separation of compounds **10c** and **10d**. The structure of compound **10c** was derived from the ^{1}H NMR analysis of the crude reaction mixture.

In compound **10c** the three NCH protons have approximately the same chemical shift (δ = 3.60), the effect of the amide carbonyl group on the two N–CH_2 protons now being equal. The MeCO substituent is found as a singulet at δ = 2.21. After column chromatography on silicagel with EtOAc as an eluent only impure **10d** was isolated. In compound **10d** again the deshielded secondary N–CH proton is found as a multiplet at δ = 4.98, the tertiary proton at δ = 3.34, while the CH_3 signal is found as a doublet around δ = 1.11.

Compound **10c** had decomposed completely during column chromatography.



9c: 10% n = 1 **9d**: 90%
10c: 85% n = 2 **10d**: 15%



11c: n = 1
12c: n = 2

Fig. 4.

Ring strain effects are no longer important in the cyclisation of the ethoxylactams **11b** and **12b**. The reaction proceeds via a linear vinyl-cation-like transition state and the 5/6 resp. 6/6 fused azabicyclics **11c** and **12c** are formed in about 90% yield each. In both cyclisations a 9:1 mixture of acetyl sidechain epimers was obtained, the ratio of which remains unchanged upon treatment with base. In the epimer mixture of compounds **12c** the major stereoisomer (equatorial sidechain) was purified by column chromatography. The major epimer of **11c** was purified and characterised by crystallisation of its tosylhydrazone.

The (pseudo) equatorial position of the acetyl group in the major epimers of **11c** and **12c** was immediately apparent from the width of the tertiary N–CH signal, possessing a large (pseudo) axial–axial coupling with the CH–COMe proton.

Although kinetic measurements were not carried out, the cyclisations of the Me-substituted acetylenes seem to be much faster than the corresponding unsubstituted acetylenes, e.g. cyclisations of **10b**, **11b** or **12b** were completed within 18 hr.

DISCUSSION

The synthesis of N-bridgehead bicyclic ketones via α-acyliminium ion-acetylene cyclisations is both versatile and practical. With terminal unsubstituted acetylenes the method allows the high yield synthesis of fused bicyclic ketones containing 6,7- or 8-membered rings. In view of the smooth cyclisation of the series of successive alkyne homologs, of which the unprecedented formation of medium sized rings is of practical and theoretical interest, the synthesis of higher membered rings via this route may also be envisaged. The starting compounds (acetylenic alcohols, N-substituted imides and ω-ethoxylactams) are mostly easily accessible.

With the abovementioned electronically biased acetylenes only k-*endo*-Dig type of cyclisations are observed (k = 6, 7, 8). 5-*endo*-Dig ringclosures could not be induced under the reaction conditions studied.

In the case of electronically unbiased acetylenes, two modes of ringclosure are competing, viz. k-*endo*-Dig vs (k − 1)-*exo*-Dig cyclisations. According to the Baldwin classification both cyclisation modes are termed as favoured processes for the ω-ethoxylactams studied (k = 6, 7).

The actual outcome of the cyclisation reaction is governed by two important factors: (i) the observed order of stability of *exo*- and *endo*-vinyl cations and (ii) ring strain effects in the resulting products. Generally, in cationic cyclisations with electronically unbiased acetylenes, the observed mode of ringclosure is of the (*k* − 1)-*exo*-Dig type due to the large difference in stability between linear and bent vinyl cations.[14] Examples are the 5-membered D-ring formation in steroid synthesis,[15] hydrindan formation[16] via acetylene-cation cyclisation, epoxy-acetylene cyclisations,[17], the iminium ion-acetylene cyclisation[18] in the tetrahydro-β-carboline series and our own results leading to the acetyl substituted azabicyclics **11c** and **12c**.

Ring strain effects become important in the cyclisations of the ethoxylactams **9b** and **10b**. In the cyclisation of **10b** a 5-*exo*-Dig type of ringclosure nevertheless is the preferential mode of cyclisation. The ring strain effects presumably account for the formation of 15% of 6/6 fused product. Similar results[16] were reported in the cation-acetylene cyclisations leading to simple hydrindan systems as a model for steroid C/D ring fusion. Cyclisation experiments conducted with systems containing an additional B-ring exclusively furnished cyclisation products with a 5-membered D ring.

Cyclisation of **9b** proceeds predominantly via a 6-*endo*-Dig[19] mode of ring closure, ring strain effects obviously having a marked influence on the transition state of the reaction. Thus, the formation of a 5/6 fused product is the major process in spite of the greater stability of the linear *exo*-vinyl cation.

α-Acyliminium ion-acetylene cyclisations inducing 5-membered ring formation deserve special attention. Attempts to synthesise 6/5 and 5/5 fused heterocyclics via 5-*endo*-Dig ring closures failed under the reaction conditions studied. However, the use of electronically biased disubstituted acetylenes can lead to the exclusive formation of N-bridgehead 5/5 fused pyrrolyzidines[21] via 5-*exo*-Dig mode of ring closure.

The application of α-acyliminium ion-acetylene cyclisations promises to be a great value in the synthesis of natural products or their analogs. An illustration of the synthetic potential of the technique is found in the synthesis[22] of the alkaloid mesembrine, the α-acyliminium ion-acetylene cyclisation being the keystep of the synthesis.

Of remarkable interest also is the synthesis[23] of a $\Delta^{8,9}$-13-azasteroid via consecutive acetylene and aryl cyclisations. Obviously, the study of acetylene cyclisations in which the intermediate vinyl cation is captured by nucleophiles other than HCOOH will expand the scope of the method considerably.

EXPERIMENTAL

IR spectra were recorded on Unicam SP 200 and Perkin–Elmer 257 instruments. ^{1}H NMR spectra were taken on Varian A-60, HA-100 and XL-100 instruments. M.ps are uncorrected. Microanalyses were carried out by Messr. H. Pieters of the microanalytical department of our laboratory. High resolution mass spectral data were recorded on a Varian Matt 711 spectrometer by Messrs. R. H. Fokkens and Dr. J. van der Greef.

Preparation of alkynols. 2-propyne-1-ol and 3-butyne-1-ol were commercially available. 3-Pentyne-1-ol was prepared from methylacetylene and oxirane according to a known procedure.[24] 4-pentyne-1-ol was prepared from tetrahydro-furfurylalcohol.[24] Methylation ($LiNH_2$, MeI) of the THP-ether of 4-pentyne-1-ol followed by deprotection afforded 4-hexyne-1-ol. 5-Hexyne-1-ol was prepared from tetrahydropyran-2-methanol according to a known procedure.[25]

Preparation of the imides. The imides were prepared according to the procedure of Mitsunobu *et al.*[26] 1 eq of alkynol, 1 eq of ϕ_3P and 1.2–1.4 eq of succinimide resp. glutarimide were dissolved in THF (freshly destilled from $LiAlH_4$). To the cooled and stirred soln 1 eq of dimethylazodicarboxylate in THF was added slowly. Stirring was continued overnight at room temp. The solvent is then evaporated under reduced pressure and the residual oil is taken up in $CHCl_3$ and 5% KOH aq. The aqueous layer is extracted 3 times with $CHCl_3$. The combined organic layers are then washed with 2N HCl (4 times) dil $NaHCO_3$ aq and sat NaCl aq, dried over $MgSO_4$ and concentrated under reduced pressure. The residual oil is dissolved in EtOAc, upon which the $\phi P \rightarrow O$ crystallises. The imides (Table 1) were obtained by vacuum-destillation (I) or column chromatography (II) and were used as such in the $NaBH_4/H^+$ reduction.

General procedure for the synthesis of ethoxylactams.[27] The $NaBH_4/H^+$ reductions were carried out with a stirred soln of the imide in EtOH at temps. of −15 to −10° (for glutarimides) and 0–5° (for succinimides) with an excess of $NaBH_4$. At regular intervals (mostly 12 min) 2–3 drops of 2N HCl in EtOH were added. The reaction time was 4–5 hr. The excess $NaBH_4$ was

Table 1. Preparation of imides

Compound	yield[a]	method[b]	phys.constants	IR[d]	^{1}H NMR data[e] NCH_2[f]	CH_2CO[g]	C≡CH[h]	C≡C-CH_3[h]
1a	59	I	128–136°/0.03 mm	1785 1715	4.28(d)	2.80	2.23	-
2a	76	I	130–140°/0.04 mm	1725 1685	4.53(d)	2.69	2.27	-
3a	29	I	95–100°/0.02 mm	1775 1705	3.69	2.72	2.01	-
4a	54	I	95–98° /0.01 mm	1720 1670	3.85	2.55	1.85	-
5a	30	II[c]	-	1780 1705	3.60	2.66	1.93	-
6a	55	I	110°/0.02 mm	1715 1660	3.75	2.53	1.80	-
7a	83	I	110°/0.005 mm	1770 1695	3.49	2.67	1.92	-
8a	70	I	116–120°/0.007 mm	1720 1665	3.67	2.57	1.84	-
9a	32	II[c]	-	1780 1705	3.50	2.58	-	1.67
10a	60	I	120–126°/0.04 mm	1720 1670	3.76	2.59	-	1.69
11a	87	II[c]	-	1775 1700	3.54	2.64	-	1.72
12a	41	I	130°/0.03 mm	1720 1670	3.88	2.66	-	1.79

a) not optimized.

b) method of preparation (I, II) indicated in the experimental.

c) column chromatography on silicagel with $CHCl_3$/aceton 19:1 as an eluent.

d) imide CO absorptions in cm^{-1}, solvent $CHCl_3$.

e) compounds 5a, 6a, 8a and 12a solvent CCl_4; other compounds solvent $CDCl_3$.

f) all triplets (unless otherwise indicated).

g) singlets for succinimides, triplets for glutarimides.

h) all triplets.

destroyed in about 15 min at −40° by adding acid till pH = 3. The mixture was stirred for an additional 1 hr at 0–5° and poured into dil $NaHCO_3$ aq. Extraction with $CHCl_3$ and work-up of the extract afforded the crude product. The products were purified by column chromatography on silicagel (act II) with EtOAc as an eluent (unless otherwise indicated).

General procedure for the cyclisation reaction. The ethoxylactam is dissolved in HCOOH and the soln is stirred at room temp. for X days. Then H_2O is added and the soln is stirred for an additional 2–3 hr at room temp. to hydrolyse the intermediate vinylformate ester. The solvent is evaporated under reduced pressure at ambient temp. The residual oil is dissolved in $CHCl_3$ and washed with dil $NaHCO_3$ aq dried over $MgSO_4$ and concentrated under reduced pressure. The crude reaction mixture is subjected to ^{1}H NMR and IR analysis. The major product or a derivative is purified (column chromatography or crystallisation) and characterized by its ^{1}H NMR and IR spectral data. Also satisfactionary analytical or high resolution mass spectral data were obtained.

1-(2-*Propynyl*)-5-*ethoxy-pyrrolidone*-2 (1b). Compound 1a (3.42 g, 25.0 mmole) was reduced in EtOH (200 ml) with 6 g of $NaBH_4$ at 0° during 4 hr. Work-up and column chromatography afforded 1.8 g (10.8 mmole) of 1b as an oil, yield: 43%. IR($CHCl_3$): 1690 cm^{-1} (CO), 3320 cm^{-1} (C≡C–H). ^{1}H NMR: δ($CDCl_3$): 5.05–5.17 (m, 1H, CHOEt) 3.61–4.60 (m, AB part of ABX system, 2H, NCH_2) 3.53 (q, 2H, OCH_2) 1.17 (t, 3H, CH_3) 1.75–2.75 (m, 5H). An exact mass determination gave *m/e* 167.0938 (Calc. for $C_9H_{13}NO_2$: 167.0941).

1-(2-*Propynyl*)-6-*ethoxy-piperidone*-2 (2b). Compound 2a (3.24 g, 21.4 mmole) was reduced in EtOH (200 ml) with 6 g of $NaBH_4$ at −12° during 5 hr. Work-up and column chromatography afforded 3.3 g (18.2 mmole) of 2b as an oil, yield: 85%. IR($CHCl_3$): 1650 cm^{-1} (CO), 3320 cm^{-1} (C≡C–H). ^{1}H NMR: δ($CDCl_3$): 4.49 (m, 1H, CH OEt) 3.72–4.98 (m, AB part of ABX system, 2H, NCH_2) 3.49–3.70 (q, 2H, O-CH_2-*Me*) 1.53–2.70 (*m*, 7H) 1.28 (t, 3H, CH_3). An exact mass determination gave *m/e* 181.1099 (Calc. for $C_{10}H_{13}NO_2$, 181.1101).

1-*Azabicyclo*[4.3.0]*nonane*-4,9-*dione* (3c)

(a) 1-(3-*Butynyl*)-5-*ethoxy-pyrrolidone*-2 (3b). Compound 3a (3.21 g, 21.3 mmole) was reduced in EtOH (300 ml) with 6 g of $NaBH_4$ at 0° during 4 hr. Work-up and column chromatography on silica gel (act I) with $CHCl_3$/acetone 4:1 as an eluent afforded 3.40 g (18.8 mmole) of 3b as an oil, yield: 88%. IR($CHCl_3$): 1685 cm^{-1} (CO), 3350 cm^{-1} (C≡C–H). ^{1}H NMR: δ ($CDCl_3$): 5.13 (m, 1H, CHOEt) 3.2–3.8 (m, 4H, OCH_2 + NCH_2) 2.00–2.80 (m, 6H) 2.00 (t, 1H, C≡C–H) 1.24 (t, 3H, O-CH_2-CH_3).

(b) *Cyclisation of* 3b. Compound 3b (500 mg, 2.76 mmole) was dissolved in 10 ml of HCOOH and stirred for 72 hr at room temp. Work-up afforded 412 mg (2.70 mmole) of 3a as an oil, which crystallised upon standing, yield: 97%, m.p. 53–57°. IR($CHCl_3$): 1710, 1680 cm^{-1} (CO). ^{1}H NMR: δ ($CDCl_3$): 4.30–4.58 (m, 1H, deshielded sec N-CH) 3.69–4.01 (m, 1H, tert N-CH) 1.55–3.19 (m, 9H) (Found: C, 62.9; H, 7.1; N, 9.1. $C_8H_{11}NO_2$ M = 153.18. Calc.: C, 62.72; H, 7.24; N, 9.14%).

1-*Azabicyclo*[4.4.0]*decane*-2,8-*dione* (4c)

(a) 1-(3-*Butynyl*)-6-*ethoxy-piperidone*-2 (4b). Compound 4a(4.0 g, 24.2 mmole) was reduced in EtOH (200 ml) with 4.6 g of $NaBH_4$ at −12° during 5 hr. Work-up and column chromatography afforded 3.93 g (20.1 mmole) of 4b as an oil, yield: 83%. IR($CHCl_3$): 1640 cm^{-1} (CO), 3310 cm^{-1} (C≡C–H). ^{1}H NMR: δ($CDCl_3$): 4.73 (m, 1H, CHOEt) 3.04–3.88 (m, 4H, OCH_2 + NCH_2) 1.14 (t, J = 7 Hz, 3H, O-CH_2-CH_3) 1.40–2.75 (m, 9H).

(b) *Cyclisation of* 4b. Compound 4b (100 mg, 0.513 mmole) was dissolved in 50 ml of HCOOH and stirred for 92 hr at room temp. Work-up afforded 76 mg (0.455 mmole) of 4c as an oil, yield: 89%. IR($CHCl_3$): 1635 and 1720 cm^{-1} (CO). ^{1}H NMR: δ($CDCl_3$) 4.75–5.02 (m, 1H, deshielded sec NCH) 3.54–3.88 (m, 1H, tert N–CH) 1.45–3.08 (m, 11H). Compound 4c was charac-

terised as its 2,4-DNP-hydrazone: m.p. 224–227° (dec). (Found: C, 52.0; H, 5.0; N, 20.0. $C_{15}H_{17}N_5O_5$ M = 347.33. Calc.: C, 51.87; H, 4.93; N, 20.17%).

1-*Azabicyclo*[5.3.0]*decane*-5-10-*dione* (**5c**)

(a) 1-(*4-Pentynyl*)-*5-ethoxy-pyrrolidone*-2 (**5b**). Compound **5a** (1.05 g, 6.2 mmole) was reduced in EtOH (100 ml) with 2.25 g of $NaBH_4$ at 0° during 4 hr. Work-up and column chromatography afforded 1.10 g (5.4 mmole) of **5b** as an oil, yield 87%. IR($CHCl_3$): 1690 cm^{-1} (CO), 3310 cm^{-1} (C≡C–H). ^1H NMR: δ($CDCl_3$): 4.98 (m, 1H, CH OEt) 3.10–3.70 (m, 4H, $NCH_2 + OCH_2$ 1.65–2.74 (m, 9H) 1.23 (t, 3H, CH_3).

(b) *Cyclisation of* **5b**. Compound **5b** (101 mg, 0.52 mmole) was dissolved in 40 ml of HCOOH and stirred for 5 days at room temp. Work-up afforded 79 mg (0.47 mmole) of **5c** as an oil which crystallised upon standing, yield: 90%, m.p.: 81–83°. IR($CHCl_3$): 1680 cm^{-1} + 1710 cm^{-1} (shoulder) (CO). ^1H NMR: δ ($CDCl_3$): 4.28–4.52 (m, 1H, deshielded sec NCH) 3.65–3.95 (m, 1H, tert NCH) 1.50–2.95 (m, 11H). (Found: C, 64.6; H, 7.8; N, 8.4. $C_9H_{13}NO_2$ M = 167.20. Calc.: C, 64.65; H, 7.84; N, 8.38%).

1-*Azabicyclo*[5.4.0]*undecane*-5,11-*dione* (**6c**)

(a) 1-(*4-Pentynyl*)-*6-ethoxy-piperidone*-2 (**6b**). Compound **6a** (1.01 g, 5.6 mmole) was reduced in EtOH (100 ml) with 2.25 g of $NaBH_4$ at −12° during 5 hr. Work-up and column chromatography afforded 0.80 g (3.8 mmole) of **6b** as an oil, yield: 68%. IR($CHCl_3$): 1630 cm^{-1} (CO), 3310 cm^{-1} (C≡C–H). ^1H NMR: δ (CCl_4): 4.57 (m, 1H, CH OEt) 3.03–3.71 (m, 4H, NCH_2 + OCH_2) 1.40–2.40 (m, 11H), 1.19 (t, 3H, CH_3).

(b) *Cyclisation of* **6b**. Compound **6b** (110 mg, 0.525 mmole) was dissolved in 40 ml of HCOOH and stirred for 5 days at room temp. Work-up afforded 86 mg (0.475 mmole) of **6c** as oily crystals, yield: 90%. IR($CHCl_3$): 1630 and 1705 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 4.60–4.85 (m, 1H, deshielded sec NCH) 3.65–3.95 (m, 1H, tert NCH) 1.50–2.95 (m, 13H). Compound **6c** was characterised as its 2,4-DNP-hydrazone, m.p. 200–201°. (Found: C, 53.3; H, 5.3; N, 19.2. $C_{16}H_{19}N_5O_5$ M = 361.35. Calc.: C, 53.18; H, 5.30; N, 19.38%).

1-*Azabicyclo*[6.3.0]*undecane*-6,11-*dione* (**7c**)

(a) 1-(*5-Hexynyl*)-*5-ethoxy-pyrrolidone*-2 (**7b**). Compound **7a** (1.12 g, 6.3 mmole) was reduced in EtOH (100 ml) with 1.8 g of $NaBH_4$ at 0° during 4 hr. Work-up and column chromatography on silica gel (Merck, Lobar) with EtOAc as an eluent afforded 965 mg (4.6 mmole) of **7b** as an oil, yield: 73%. IR($CHCl_3$): 1680 cm^{-1} (CO), 3320 cm^{-1} (C≡C–H). ^1H NMR: δ ($CDCl_3$) 4.90 (m, 1H, CH OEt) 2.90–3.59 (m, 4H, $NCH_2 + OCH_2$) 1.30–2.68 (m, 11H) 1.16 (t, 3H, CH_3).

(b) *Cyclisation of* **7b**. Compound **7b** (92 mg, 0.44 mmole) was dissolved in 200 ml of HCOOH and stirred for 14 days at room temp. Work-up afforded 64 mg (0.35 mmole) of **7c** as an oil, which crystallized upon standing, yield: 80%, m.p. 89–90° (isopropylether). IR(KBr): 1665 + 1690 cm^{-1} (CO). ^1H NMR: δ ($CDCl_3$): 3.65–3.98 (m, 2H, tert NCH + deshielded sec NCH) 2.91 (t, J = 11H² 1H, shielded sec NCH), 1.30–2.80 (m, 12H). (Found: C, 66.2; H, 8.5; N, 7.8. $C_{10}H_{15}NO_2$ M = 181.23. Calc.: C, 66.27; H, 8.34; N, 7.73%).

1-*Azabicyclo*[6.4.0]*dodecane*-6,12-*dione* (**8c**)

(a) 1-(*5-Hexynyl*)-*6-ethoxy-piperidone*-2 (**8b**). Compound **8a** (1.6 g, 8.3 mmole) was reduced in EtOH (100 ml) with 2.3 g of $NaBH_4$ at −12° during 5 hr. Work-up and column chromatography on silica gel (Merck, Lobar) with EtOAc as an eluent afforded 1.5 g (6.7 mmole) of **8b** as an oil, yield: 81%. IR($CHCl_3$): 1630 cm^{-1} (CO), 3320 cm^{-1} (C≡C–H). ^1H NMR: δ ($CDCl_3$): 4.57 (m, 1H, CH OEt) 2.96–3.83 (m, 4H, $NCH_2 + OCH_2$) 1.35–2.55 (m, 13H) 1.23 (t, 3H, CH_3).

(b) *Cyclisation of* **8b**. Compound **8b** (40 mg, 0.18 mmole) was dissolved in 40 ml of HCOOH and stirred for 14 days at room temp. Work-up afforded 27 mg (0.14 mmole) of **8c** as an oil, which crystallized upon standing yield: 77%, m.p. 67–68° (iprop–ether). IR($CHCl_3$): 1620 cm^{-1} (CO), 1690 cm^{-1} (CO). ^1H NMR: δ ($CDCl_3$): 4.08 (d of m, J_d = 11 Hz, 1H, deshielded sec NCH) 3.53–3.80 (m, 1H, tert NCH) 3.13 (t, J = 11 Hz, 1H, shielded sec NCH) 1.20–2.68 (m, 14H). (Found: C, 67.7; H, 8.8; N, 7.1. $C_{11}H_{17}NO_2$ M = 195.25. Calc.: C, 67.66; H, 8.78; N, 7.17%).

5-*Methyl*-1-*azabicyclo*[4.3.0]*nonane*-4,9-*dione* (**9d**)

(a) 1-(*3-Pentynyl*)-*5-ethoxy-pyrolidone*-2 (**9b**). Compound **9a** (1.2 g, 7.3 mmole) was reduced in EtOH (100 ml) with 2.7 g of $NaBH_4$ at 0° during 4 hr. Work-up and column chromatography afforded 0.85 g (4.4 mmole) of **9b** as an oil, yield: 60%. IR($CHCl_3$): 1690 cm^{-1} (CO). ^1H NMR: δ ($CDCl_3$) 5.04 (m, 1H, CH OEt) 3.05–3.75 (m, 4H, $NCH_2 + OCH_2$) 1.85–2.68 (m, 6H) 1.70 (t, 3H, C≡C–CH_3) 1.16 (t, 3H, OCH_2CH_3).

(b) *Cyclisation of* **9b**. Compound **9b** (650 mg, 3.34 mmole) was dissolved in 80 ml of HCOOH and stirred for 5 days at room temp. Work-up afforded a 9:1 mixture of compound **9d** and **9c** (500 mg, 3.10 mmole) yield: 90%. Compound **9d** crystallised from this mixture (21 mg, m.p. unrecorded). Compound **9d**: IR($CHCl_3$) 1680 cm^{-1} + 1720 cm^{-1} (shoulder) (CO). ^1H NMR: δ($CDCl_3$): 4.38–4.60 (m, 1H, deshielded sec NCH) 3.22–3.52 (m, 1H, tert NCH) 1.05 (d, 3H, CH_3) 1.60–3.15 (m, 8H). Compound **9d** was characterised as its 2,4-DNP-hydrazone, m.p. 218–220°. (Found: C, 51.9; H, 4.8; N, 20.0. $C_{15}H_{17}N_5O_5$ M = 347.33. Calc.: C, 51.87; H, 4.93, N, 20.17%).

1-(*3-Pentynyl*)-*6-ethoxy-piperidone*-2(**10b**)

Compound **10a** (1.5 g, 8.4 mmole) was reduced in EtOH (100 ml) with 2.4 g of $NaBH_4$ at −12° during 5 hr. Work-up and column chromatography afforded 1.1 g (5.3 mmole) of **10b** as an oil, yield: 63%. IR($CHCl_3$): 1640 cm^{-1} (CO). ^1H NMR: δ ($CDCl_3$) 4.76 (m, 1H, CHOEt) 3.06–3.94 (m, 4H, $NCH_2 + OCH_2$) 1.50–2.70 (m, 8H) 1.79 (m, 3H, C≡C–CH_3) 1.25 (t, 3H, OCH_2CH_3). An exact mass determination gave *m/e* 209.1413. (Calc. for $C_{12}H_{19}NO_2$: 209.1416).

Cyclisation of **10b**. Compound **10b** (487 mg, 2.3 mmole) was dissolved in 200 ml of HCOOH and stirred for 3 days at room temp. Work-up afforded 394 mg (2.1 mmole) of an 85:15 mixture of **10c** and **10d**, yield: 92%. It was not possible to separate the compounds due to decomposition during column chromatography or destillation. Also no crystalline derivatives could be obtained. IR($CHCl_3$): 1620 cm^{-1} and 1710 cm^{-1}. ^1H NMR: δ ($CDCl_3$): characteristics for **10c**: 3.45–3.80 (m, 3H, NCH_2 + NCH) 2.21 (s, 3H, CH_3CO). Characteristics for **10d**: 4.90 (m, 1H, deshielded sec NCH) 1.08 (d, 3H, Me). An exact mass determination (crude mixture) gave *m/e* 181.1092. (Calc. for $C_{10}H_{15}NO_2$: 181.1092).

5-*Acetyl*-1-*azabicyclo*[4.3.0]*nonane*-9-*one* (**11c**)

(a) 1-(*4-Hexynyl*)-*5-ethoxy-pyrrolidone*-2 (**11b**). Compound **11a** (2.03 g, 1.3 mmole) was reduced in EtOH (200 ml) with 4.5 g of $NaBH_4$ at 0° during 4 hr. Work-up and column chromatography afforded 1.18 g (5.65 mmole) of **11b** as an oil, yield: 50%. IR($CHCl_3$): 1685 cm^{-1} (CO). ^1H NMR: δ ($CDCl_3$): 4.94–5.06 (m, 1H, CH OEt) 3.07–3.73 (m, 4H, $OCH_2 + NCH_2$) 1.5–2.74 (m, 8H) 1.78 (m, 3H, C≡C–CH_3) 1.24 (t, 3H, OCH_2–CH_3).

(b) *Cyclisation of* **11b**. Compound **11b** (113 mg, 0.52 mmole) was dissolved in 40 ml of HCOOH and stirred for 24 hr at room temp. Work-up afforded 90 mg (0.495 mmole) of **11c** as an oil, yield: 92%. The C_5-epimer ratio was approximately 9:1. IR($CHCl_3$): 1675 and 1710 cm^{-1} (CO). ^1H NMR: δ ($CDCl_3$): major epimer: 4.15 (d of m, J_d = 13 Hz, 1H, deshielded sec NCH) 3.45–3.78 (m, 1H, tert NCH) 1.20–2.75 (m, 10H) 2.20 (s, 3H, CH_3CO). The major epimer was purified and characterised as its tosylhydrazone, m.p. 248° (dec). (Found: C, 58.5; H, 6.7; N, 11.9. $C_{17}H_{23}N_3SO_3$ M = 349.38. Calc.: C, 58.44; H, 6.64; N, 12.03%).

7-*Acetyl*-1-*azabicyclo*[4.4.0]*decane*-2-*one* (**12c**)

(a) 1-(*4-Hexynyl*)-*6-ethoxy-piperidone*-2 (**12b**). Compound **12a** (1.24 g, 6.4 mmole) was reduced in EtOH (100 ml) with 2.25 g of $NaBH_4$ at −12° during 5 hr. Work-up and column chromatography afforded 662 mg (2.98 mmole) of **12b** as an oil, yield: 46%. IR($CHCl_3$): 1640 cm^{-1} (CO). ^1H NMR: δ ($CDCl_3$): 4.60(m, 1H, CH OEt) 3.03–3.85 (m, 4H, $NCH_2 + OCH_2$) 1.45–2.50 (m, 10H) 1.71 (m, 3H, C≡C–CH_3) 1.19 (t, 3H, OCH_2–CH_3).

(b) *Cyclisation of* **12b**. Compound **12b** (430 mg, 1.93 mmole)

was dissolved in 50 ml of HCOOH and stirred for 72 Hr at room temp. Work-up afforded 333 mg (1.7 mmole) of 12c as an oil, yield: 88%. The C_7-epimer ratio was approximately 9:1. The major epimer could be purified by column chromatography on silicagel with $CHCl_3$/acetone 9:1 as an eluent. IR($CHCl_3$): 1620 and 1710 cm^{-1} (CO). ^1H NMR: δ ($CDCl_3$): 4.69–4.95 (d of m, J_d = 14 Hz, 1H, deshielded sec NCH) 3.30–3.36 (m, 1H, tert NCH) 1.15–2.61 (m, 12H) 2.15 (s, 3H, CH_3CO). This major epimer was characterized as its tosylhydrazone, m.p. 250° (dec). (Found: C, 59.5; H, 7.0; N, 11.6. $C_{18}H_{25}N_3SO_3$ M = 363.40. Calc: C, 59.49; H, 6.93; N, 11.56%).

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