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CYCLISATIONS OF 1,3-THIAZINE-2,4-DIONES AND RELATED SYSTEMS

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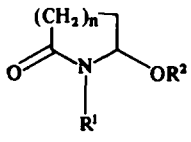
Abstract—Thiazinediones **10** and **11** serve as starting materals for intramolecular amidoalkylations. While the stability of the derived hydroxy lactams **14** and **15** is lower as compared to carbocyclic analogs the ring closures to the bicyclic systems indicate a common order of reactivity of the corresponding N-acyliminium intermediate, e.g. **26**.

In recent years the knowledge of the fundamental chemistry of the N-acyliminium ion has been greatly improved[1] and this reaction principle consitutes the basis for the total synthesis of an increasing number of natural products.[2] In addition, the methodology has been extended to the use of heterocyclic rings for the imide moiety, notably the 5-membered thiazolidine-2,4-dione unit.[3] Within the latter context the use of 6-membered heterocyclic imides, e.g. 1,3-thiazine-2,4-diones seemed of interest for a variety of reasons. The larger ring system could provide added possibilities for the introduction of functional groups; furthermore, the step from the 5-membered to the 6-membered ring is expected to be accompanied by a change in reactivity, as has been found in the carbocyclic imide system.[4] Enamide formation in glutarimide systems (i.e. **1a** → **2a**) occurs quite readily and leads to dimerisation products. The elimination, however, is encountered rarely in the succinimide series (**1b**). The presence of the S atom might enhance enamide formation if the S 3d-orbital can overlap with the π-orbitals of the double bond thus formed. This effect might cause a difference in reactivity between the two relevant thiazinediones **3** and **4**. Therefore, both were selected to study their reaction behaviour. For reference purposes, some parallel experiments have been carried out with the oxygen analog of **4**, the morpholinedione **5**.

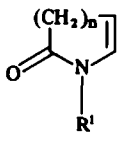
Starting materials

The starting N—H imides **4** and **5** were prepared via known methods. The unsubstituted tetrahydro-1,3-thiazine-2,4-dione[5] **3** has reportedly been synthesised, e.g. by condensation of ammonium dithiocarbamate with propiolactone[6] and oxidation of the resulting thione **6** with potassium dichromate.[7] However, the attempted conversion of **6** to **3** proved unsatisfactory. An alternative oxidation with cyclohexene epoxide[8] afforded an inseparable mixture of thione **6** and dione **3**. A second method for the synthesis of 1,3-thiazine systems consists of a condensation of thiourea with α,β-unsaturated carboxylic acids by refluxing in phosphoric acid.[9] For acrylic acid, this method gave very low yields, probably due to polymerisation of the starting material as a competing reaction. Fortunately, with a series of substituted acrylic acids better results could be obtained, thus affording the imides **7a–7d** in good to excellent yields.

Interestingly, if the same reaction is carried out with dimethyl acetylenedicarboxylate two modes of cyclisation are possible for the intermediate addition product **8**, depending on which carbonyl group will react (Fig. 1); our results (see below) indicated 5-*exo*-Trig in this case to be favoured over 6-*exo*-Trig ring closure, thereby forming the thiazolidine[10] **9b** rather than the thiazine[11] **9a**. The thiazolidine **9b** could be hydro-



1 **a** n = 2 **b** n = 1



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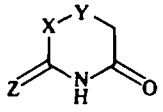
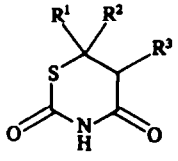


	X	Y	Z
3	S	CH_2	O
4	CH_2	S	O
5	CH_2	O	O
6	S	CH_2	S



	R^1	R^2	R^3
7a	C_6H_5	H	H
7b	CH_3	CH_3	H
7c	CH_3	H	H
7d	H	H	CH_3

Scheme 1.

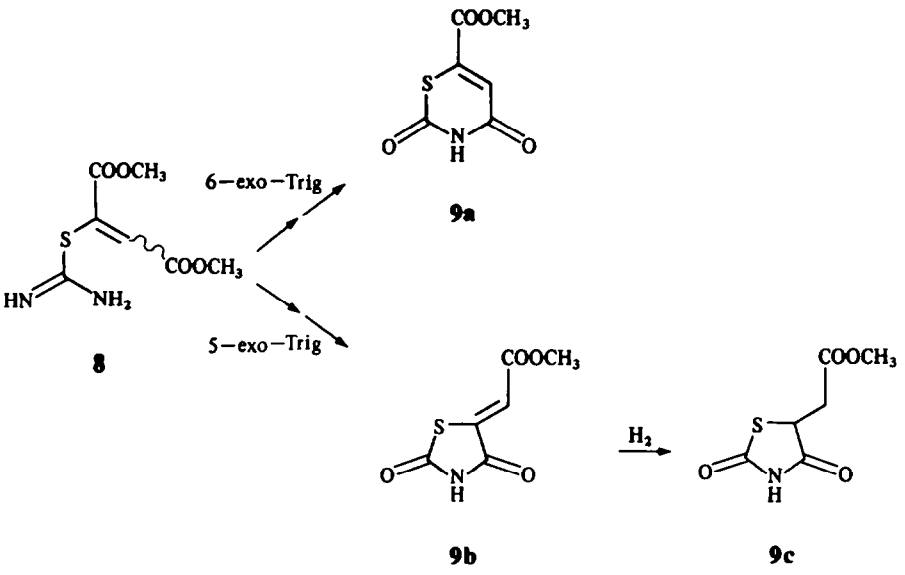


Fig. 1.

genated to **9c**; the corresponding acid could also be obtained by condensation of maleic acid and thiourea.[12]

The N—H imides thus obtained were converted to the N-substituted products **10–13** via coupling with a suitable alcohol according to the procedure of Mitsunobu *et al.*[13]

Reductions

It has been known for some time[14] that hydroxy lactams exhibit a behaviour which might be referred to as "ring-chain tautomerism"[15] (Fig. 2). Upon reduction of the imide **17** the hydroxy lactam **18a** is formed, which exists in equilibrium with the open-chain form **18b**.

If the equilibrium between **18a** and **18b** is shifted fast enough as to form an appreciable amount of the amidealdehyde **18b** the latter will be further reduced to give the amide-alcohol **19**. The position of the equilibrium is determined by a number of factors, among which is the size of the ring. Larger rings exhibit a greater tendency to give the ring opened form **18b**. Thus, hydroxyprrolidones (**18a**, X = CH_2CH_2) are more stable than hydroxypiperidones (**18a**, X = $CH_2CH_2CH_2$),[16] whereas hydroxyazepinones (**18a**, X = $CH_2CH_2CH_2CH_2$) exist in the ring-closed form only at temperatures well below 0°.[17] In general, an increasing size of the imide ring necessitates a lowering of the reaction temperature to prevent ring opening and over-reduction of the hydroxy lactam.[18] To further enhance the stability of the reduction products the hydroxy lactams are converted to the ethoxy lactams **18c**, which can be chromatographed and stored without decomposition. Ethoxy lactams are also excellent precursors for generation of the acyliminium species.

As has been found[3] before, thiazolidine hydroxy lactams are very stable in this respect: no trace of the ring opened tautomer has ever been detected. From the considerations mentioned above, however, it might be anticipated that the larger ring size of the thiazine imides would possibly promote formation of the open-chain form. Consequently, reductions were carried out at lower temperatures. Nevertheless, reduction of the 1,4-thiazines **10a** and **10b** at −20° generally afforded mixtures of products which could not be identified; probably mostly open chain products **20** were present, accompanied by enamide. On the contrary on reduction of **11a** the lactam **15a** could be obtained[19] in a

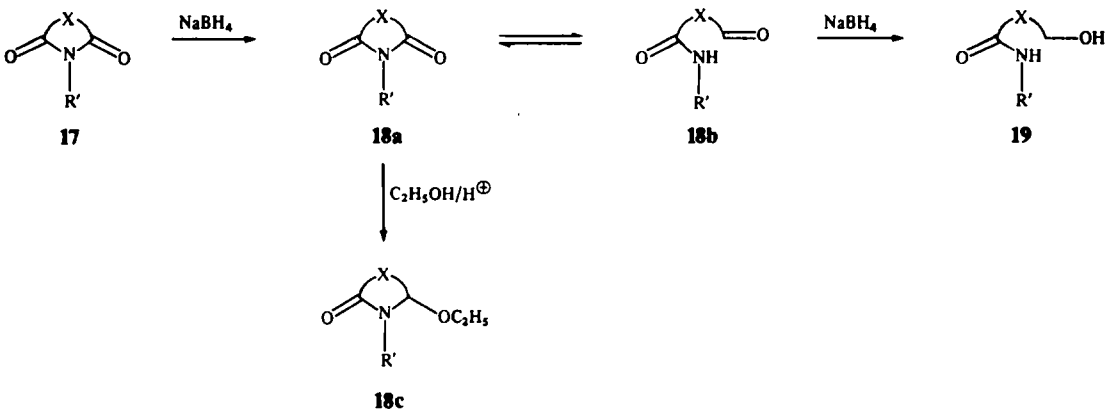
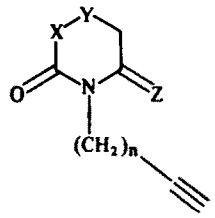
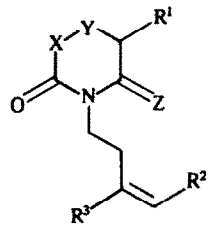


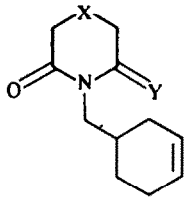
Fig. 2.



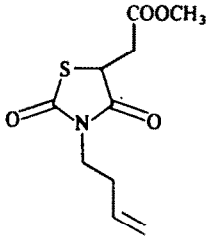
		n	X	Y	R
10 Z = O	**a**	2	CH_2	S	–
14 Z = H,OR	**b**	4	CH_2	S	–
	c	4	CH_2	O	H
	d	2	S	CHC_6H_5	C_2H_5
	e	2	S	$C(CH_3)_2$	C_2H_5

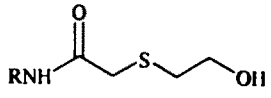


		X	Y	R^1	R^2	R^3	R^4
11 Z = O	**a**	CH_2	S	H	H	CH_3	H
15 Z = H,OR^4	**b**	CH_2	O	H	C_2H_5	H	H
	c	S	CHC_6H_5	H	H	H	C_2H_5
	d	S	CHC_6H_5	H	C_2H_5	H	C_2H_5
	e	S	CH_2	CH_3	H	H	–
	f	S	$CHCH_3$	H	H	H	–
	g	S	$CHCH_3$	H	C_2H_5	H	–



a X = S
b X = O

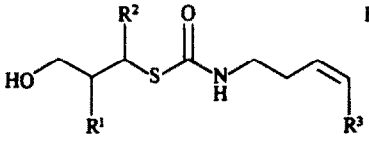




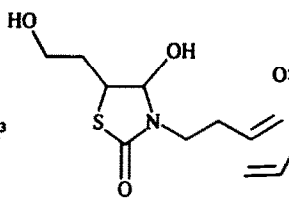
12 Y = O
16 Y = H,OH

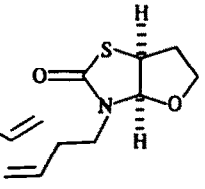
13

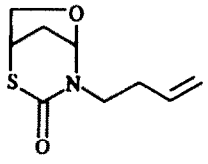
20



	R^1	R^2	R^3
21a	H	CH_3	H
b	H	CH_3	C_2H_5
c	CH_3	H	H







22

23a

23b

Scheme 2.

surprisingly high yield of 92%. In addition the oxazines **10c** and **11b** could be reduced smoothly at temperatures of −30 to −15° affording the corresponding hydroxy lactams **14c** and **15b** in yields of 60–90%. This stability of the hydroxyoxazinones relative to the hydroxythiazones is attributed to a difference in ring size, the C—S bond length (1.81 Å, as compared to 1.41 Å for the C—O bond)[20] making the thiazine almost comparable to a seven-membered ring.[21]

In view of the results of the 1,4-thiazines, the reductions of the 1,3-thiazines **10d**, **10e** and **11c–11g** were carried out at temperatures of −30 to −15°[22] and care was taken to convert the hydroxy lactams, if formed at all, to the corresponding ethoxy lactams, to enhance stability during work-up and purification.

Accordingly, the ethoxy lactams **14e**, **15c** and **15d** could be obtained in yields of over 90%. The remaining thiazinediones **10d** and **11e–11g** afforded ring opened products of type **21**, of which **21a–21c** could be obtained pure and in high yields. The structures were evident

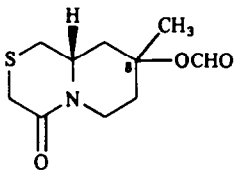
from the spectral data: the presence of an OH-absorption at 3400 cm^{-1} in the IR spectrum, the ^1H-NMR integrated values, while the absence of the triplet/quartet signals from the Et group in the ^1H-NMR indicated the absence of an ethoxy lactam. Ring opening appeared not to be related to the temperature at which the reduction was carried out, e.g. **15d** was obtained at a reduction temperature of $-10°$, whereas **15g** gave open chain products both upon reduction at $-10°$ and at $-70°$. The unexpectedly large and unpredictable influence of minor changes in substituent pattern on the ease of ring opening, e.g. the difference between **10a** and **11a**, renders an explanation of this behaviour rather difficult.

An interesting result was obtained upon $NaBH_4$ treatment of **13**. A product **22** was obtained in which the ester group has also been reduced. The latter process occurs normally only under special circumstances.[23–26] However, in this case reduction of the ester is probably assisted by the proximity of the functionalities in the ring system.[27] Upon treatment of **22** with acetic acid/acetic anhydride a new compound was obtained which, after NMR decoupling experiments, was proven to be **23a**. Prominent features in the ^1H-NMR spectrum are a doublet at 5.61 ppm, J = 7 Hz of the NCHO proton, and a triplet at 4.19 ppm, J = 7 Hz of the SCH bridgehead proton. Irradiation of the NCHO signal changed the triplet to a doublet, J = 7 Hz; conversely, irradiation of the signal at 4.19 ppm changed the absorption at 5.61 ppm to a singlet besides causing a change in the signals around 2.2 ppm (S—CH—CH_2) protons. This outcome also excludes a 6-membered structure **23b**, which would originate from thiazine **9a**. Clearly **22**, which can be viewed upon as a N,O-hemiacetal, is converted, under the circumstances employed, to the N,O-acetal **23a**; in fact, this is an intramolecular analogy of the ethoxy lactam formation.

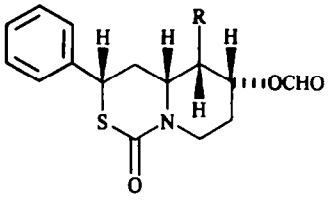
Cyclisations

The hydroxy or ethoxy lactams mentioned above were cyclised by stirring in formic acid.

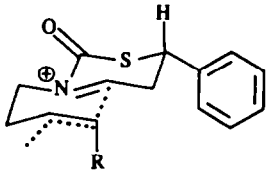
Reaction of the 1,4-thiazine hydroxy lactam **15a** in formic acid (room temperature 16 hr) afforded a mixture of epimers **24**[28] in a ratio of about 4 : 1, one of which was obtained in 55% yield after chromatography. The



24a C_8—$CH_3\beta$
24b C_8—$CH_3\alpha$



25a R = H
25b R = C_2H_5



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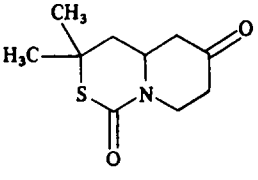

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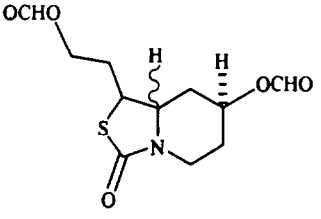

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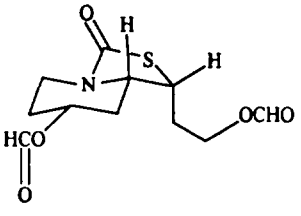

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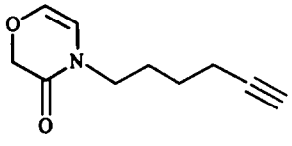

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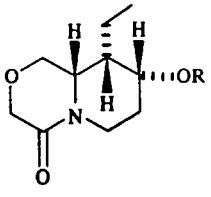
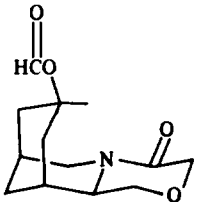


31a R = CHO
31b R = H



32

Scheme 3.

relative configuration of this compound could not be established with certainty; however, from analogous cyclisations in the glutarimide series[29] the epimer **24a** is expected to be the major component.

Cyclisations of the 1,3-thiazines **15c** and **15d** afforded products **25a** (HCOOH, room temperature, 15 hr, yield 50%) and **25b** (HCOOH, room temperature 67 hr, yield 86%) with relative configurations as shown, indicating a transition state **26** with "double chair" configuration, in which the phenyl group occupies an equatorial position. The stereochemistry again was determined from first order analysis of the ^{1}H-NMR spectrum, as will be discussed for **25b**. The signal of the NCH bridgehead proton at 3.72 ppm (ddd, J = 10.5, 6 and 2.5 Hz) indicates only one axial–axial coupling, thereby pointing to an axial position for the Et group, while the signal for the CHOCHO proton at 5.11 ppm, which has a width of 29 Hz, indicates at least one axial–axial coupling to be present, leaving the formyloxy group to occupy an equatorial position. Finally, the $SCHC_6H_5$ signal at 4.46 exhibits a double doublet, J = 10.5 and 3.5 Hz, which is consistent with an equatorial phenyl group. Further signals include the deshielded equatorial NCH_2 proton at 4.83 ppm (J = 14.0, 5.0 and 3.0 Hz) and the corresponding shielded axial proton at 2.75 ppm. Likewise, upon prolonged treatment of **14e** (HCOOH, room temperature, 7 days) **27** could be obtained in 45% yield. Thus, the reaction behaviour of a set of π-nucleophiles against this type of acyliminium ion corresponds to that of the thiazolidines.[3]

Whereas ethoxy lactams upon acid treatment readily yield the acyliminium ion, the cyclic alkoxy lactam **23a** proved remarkably unreactive, corroborating the general observation that cyclic acetals are hydrolysed with more difficulty than open chain ones.[30] However, treatment with formic acid at 60° overnight afforded **28** as a 2 : 1 mixture of C-4 epimers of which **29** is the major isomer. This is concluded from the signal at 5.2–4.8 ppm of the CHOCHO proton, $W_{\frac{1}{2}}$ = 33 Hz and from the NCH bridgehead absorption at 3.48 ppm containing an axial–axial coupling.

The hydroxy lactams obtained in the oxazine series also were subjected to standard cyclisation conditions. The hexyne-substituted **14c** upon HCOOH treatment (room temperature, 3 days) gave, in addition to starting material, about 25% of the dihydrooxazine **30**, as was evident from the ^{1}H-NMR spectrum, which showed an AB signal at 6.20 and 5.61 ppm, J = 4.5 Hz. Prolonged treatment (10 days at 43°) did not improve the result, and mainly decomposition occurred.

On the contrary, **15b** cyclised (HCOOH, room temperature, 70 hr) smoothly and stereoselectively, giving **31a** in quantitative yield. Hydrolysis of **31a** afforded the crystalline alcohol **31b**. Similarly, **16b** was cyclised (HCOOH, room temperature, 19 hr) to afford **32** in 71% yield. The rearranged position (C-10 to C-11) of the formate moiety[29] is inferred from its equatorial position, which is apparent from the ^{1}H-NMR signal of the CHOCHO proton (5.55–5.15 ppm), and also from the observation[31] that 3-aza-bicyclo[3.3.1]nonanes prefer the "double chair" conformation.

CONCLUSION

The reactivity of hydroxy lactams derived from heterocyclic 6-membered cyclic imides in general parallels that found in the thiazolidine series. The larger ring size of the thiazine ring system, which nearly equals a 7-membered ring, renders the hydroxy lactams derived from these compounds relatively unstable, giving rise to ring opening and other unwanted side reactions. On the contrary, the hydroxy lactams in the oxazine series possess a stability comparable to that encountered in the thiazolidine series. If hydroxy or ethoxy lactams can be formed, however, cyclisation products can be obtained often in a stereoselective fashion.

EXPERIMENTAL

IR spectra were recorded on Unicam SP 200 and Perkin–Elmer 257 instruments. ^{1}H-NMR spectra were obtained with Varian A-60, HA-100, XL-100 and Bruker WM 250 instruments. Spectra were recorded in $CDCl_3$, unless otherwise indicated, and signals are given in ppm relative to TMS as an internal reference. All mass spectral data were recorded on an AEI-ms-902 or Varian Mat 711 mass spectrometer. M.p.s were determined on a Leitz m.p. microscope and are incorrected. Micro-analyses were carried out by TNO, Utrecht, The Netherlands. In naming the compounds, IUPAC nomenclature is used.

Preparation of starting materials

Compound **3** was prepared by heaing thio-diglycolic anhydride with NH_4OH.[32] Likewise, **5** was obtained from diglycolic anhydride. Substituted **7** were prepared[9] by heating the appropriate acrylic acid with 1 equiv thiourea to 160° in 40% phosphoric acid overnight; upon cooling, the thiazine crystallised. Compound **9c** was obtained by adding 1 equiv of dimethyl acetylenedicarboxylate to a cooled soln of thiourea in 40% H_3PO_4 and refluxing for 90 min; the ppt obtained after cooling was subsequently hydrogenated (Pd/C, EtOH). 5-Hexyn-1-ol was prepared from tetrahydropyran-2-methanol.[33] All other compounds were commercially available.

Preparation of imides

Imides were prepared[13] by slowly adding 1 equiv of dimethyl azodicarboxylate in freshly distilled THF to a cooled and stirred soln of 1 equiv of NH imide, 1 equiv of the appropriate alcohol and 1 equiv of triphenylphosphine. Stirring was continued at room temp overnight. The solvent was then evaporated under reduced pressure, and the residual oil taken up in CH_2Cl_2 and 5% KOH aq. The aqueous layer was extracted three times with CH_2Cl_2; the combined organic layers were then washed twice with 2 N HCl, sat $NaHCO_3$ aq and sat NaCl aq, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was taken up in EtOAc, upon which the triphenylphosphine oxide formed partly crystallised. The coupled imides were then obtained by vacuum distillation or column chromatography. For specific details, see Table 1.

General procedure for reduction of imides

The imide is dissolved in EtOH, cooled to the temp specified, and 2 equiv by wt of $NaBH_4$ added, after which the cooled soln is stirred for 4 hr, while 3 drops of ethanolic HCl (pH 2) are added every 15 min. The mixture is then worked up or the hydroxy lactam is converted to the ethoxy lactam by lowering the temp to −35° and acidifying to pH 2 after which the soln is stirred for another hr. The soln is then poured into ice-cold sat $NaHCO_3$ aq, extracted four times with CH_2Cl_2, the combined organic layers washed with sat NaCl aq, dried over Na_2SO_4 and, after evaporation of the solvent, purified by column chromatography or recrystallisation.

General procedure for the cyclisation reaction

The hydroxy or ethoxy lactam is dissolved in formic acid and stirred at the temp specified. The solvent is evaporated under reduced pressure, the residue taken up in CH_2Cl_2 and

Table 1. Preparation of *N*-substituted imides

Imide	Yield (%)	Procedure for purification[a]	b.p.	m.p.[b]	IR (cm^{-1})[c]	^{1}H-NMR data (ppm) NCH$_2$	CH$_x$=CH$_y$	C≡CH
10a	34	vd	102°/0.01 mm	—	1670/1725	4.02	—	1.96
10b	28	vd	132°/0.02 mm	—	1665/1720	3.83	—	1.91
10c	69	vd	120°/0.02 mm	—	1690/1745	3.78	—	1.96
10d	66	cg[d]	—	60–61°	1650/1715	4.14	—	2.01
10e	63	vd	100°/0.1 mm	45–48°	1650/1715	4.15	—	1.97
11a	33	vd	122°/0.1 mm	—	1670/1720	3.94	4.72	—
11b	75	vd	98°/0.02 mm	—	1685/1745	3.83	5.65–5.10	—
11c	33	vd	150°/0.06 mm	72–74°	1645/1715	4.00	6.00–4.80	—
11d	60	cg[e]	—	42–44°	1650/1710	3.99	5.65–5.20	—
11e	30	vd	114°/0.2 mm	—	1640/1705	3.98	6.20–4.80	—
11f	70	vd	81°/0.11 mm	—	1640/1710	3.99	6.20–4.85	—
11g	74	vd	107°/0.08 mm	—	1640/1710	3.96	5.80–5.10	—
12a	68	vd	128°/0.04 mm	78–80°	1670/1720	3.80	5.67	—
12b	54	vd	104°/0.06 mm	38–40°	1690/1740	3.77	5.66	—
13	43	vd	90°/0.05 mm	—	1680/1740	3.73	6.10–4.90	—

[a] Procedure for purification: cg = column chromatography, vd = vacuum distillation.
[b] From dipe (= diisopropylether).
[c] Carbonyl absorption.
[d] On silica, eluent dichloromethane–acetone 4:1.
[e] On silica, eluent dichloromethane–acetone 1:1.

washed with sat $NaHCO_3$ aq, water, and sat NaCl aq, dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product.

6-*Aza*-1-*hydroxy*-3-*methyl*-4-*thiadec*-9-*en*-5-*one* **21a**. Compound **11f**, 4.5 g (22.6 mmol) was reduced with 9 g (0.24 mol) $NaBH_4$ at −10°. The oil obtained after work-up was purified by column chromatography (silica, eluent CH_2Cl_2–acetone 4:1), giving 3.3 g (73%) **21a** as a clear oil. IR ($CHCl_3$): 3420 cm^{-1} (OH); 1645 cm^{-1} (CO); ^{1}H-NMR: 6.1–4.9 (m, 4H, CH=CH$_2$ and NH), 4.05–3.20 (m, 6H; 5H, sharpened upon addition of D_2O; NCH$_2$, OCH$_2$, SCH and OH), 2.5–1.2 (m, 4H), 1.37 (d, 3H, CH_3).

(Z)-6-*Aza*-1-*hydroxy*-3-*methyl*-4-*thiadodec*-9-*en*-5-*one* **21b**. Compound **11g**, 4.6 g (20.3 mmol) was treated as above, affording 3.30 g (73%) **21d**. IR ($CHCl_3$): 3420 cm^{-1} (OH); 1645 cm^{-1} (CO); ^{1}H-NMR: 6.05–5.0 (m, 3H; 2.5H upon addition of D_2O; CH=CH and NH), 4.05–3.15 (m, 6H; 5H, sharpened with D_2O; NCH$_2$, HOCH$_2$ and SCH), 2.55–1.30 (m, 6H), 1.39 (d, 3H, CH_3), 0.97 (t, 3H, CH_3). An accurate mass determination gave 231.12929; $C_{11}H_{21}NO_2S$ requires 231.12928.

6-*Aza*-1-*hydroxy*-2-*methyl*-4-*thiadec*-9-*en*-5-*one* **21c**. Compound **11e**, 3.8 g (19.1 mmol) was reduced as above with 7.6 g (0.2 mol) $NaBH_4$ to give 3.47 g (90%) **21c** as an oil. IR ($CHCl_3$): 3425 cm^{-1} (OH); 1650 cm^{-1} (CO); ^{1}H-NMR: 6.35–5.5 (m, 2H; 1H with D_2O; C<u>H</u>=CH$_2$ and NH), 5.35–4.85 (m, 2H, CH=C<u>H</u>$_2$), 3.8–2.9 (m, 7H; 6H upon additon of D_2O; NCH$_2$, SCH$_2$ and CH$_2$OH), 2.5–1.65 (m, 3H), 0.93 (d, 3H, CH_3). An accurate mass determination gave 203.09799; $C_9H_{17}NO_2S$ requires 203.09798.

8-*Formyloxy*-8-*methyl*-1-*aza*-4-*thiabicyclo*[4.4.0]*decan*-2-*one* **24**. (a) 4-(3-Methyl-3-butenyl)-5-hydroxytetrahydro-1,4-thiazin-3-one (**15a**). 0.82 g (4.1 mmol) **11a** was reduced with 1.80 g (47 mmol) $NaBH_4$ at −20°. Work-up afforded 0.76 g oil (92% yield) which crystallised upon cooling; m.p. 39–42° (from dipe). IR ($CHCl_3$): 3480 cm^{-1} (OH); 1635 cm^{-1} (CO); ^{1}H-NMR: 4.99 (d, 1H, s with D_2O, C<u>H</u>OH), 4.73 (d of m, 2H, CH$_2$=), 3.90–3.65 (m, 3H; 2H upon addition of D_2O; OH and NCH$_2$), 3.55–2.65 (m, 4H, SCH$_2$), 2.29 (t, 2H, NCCH$_2$), 1.77 (s, 3H, CH_3). (Calc for $C_9H_{15}NO_2S$ (Mw 201.29): C, 53.70; H, 7.51; N, 6.96; S, 15.93%. Found: C, 53.7; H, 7.5; N, 6.9; S, 15.9%.)

(b) Cyclisation of **15a**. Compound **15a** 0.248 g (1.23 mmol) was dissolved in 50 ml formic acid and stirred at room temp for 16 hr. Work-up afforded 0.221 g brown oil, a fraction of which with R_f 0.6 was isolated (silica, eluent $CHCl_3$–acetone 4:1). Yield: 155 mg (55%) of a pale oil which solidified; m.p. 87–89°. IR ($CHCl_3$): 1720 cm^{-1} (ester CO); 1620 cm^{-1} (CO); ^{1}H-NMR: 8.09 (s, 1H, OCHO), 4.75 (ddd, 1H, NCH$_2$ equiv), 3.95–3.65 (m, 1H, NCH bridgehead), 3.31 (s, 2H, SCH$_2$), 3.13–2.20 (m, 5H), 1.90–1.30 (m, 2H), 1.61 (s, 3H, CH_3). An accurate mass determination gave 229.0765; $C_{10}H_{15}NO_3S$, requires 229.07724.

3-(3-*Butynyl*)-4-*ethoxy*-6-*phenyltetrahydro*-1,3-*thiazin*-2-*one* **14d**. Compound **10d**, 5.151 g (19.9 mmol) was reduced with 11 g (0.29 mol) $NaBH_4$ and subsequently converted to the ethoxy lactam. Work-up afforded 5.0462 g of a pale green oil (88%). IR ($CHCl_3$): 3310 cm^{-1} (C≡C—H); 1660 cm^{-1} (CO); ^{1}H-NMR: 7.31 (s, 5H, Ph), 4.80 (dd, 1H, NCHO), 4.0–3.2 (m, 5H), 2.6–1.9 (m, 5H), 1.22 (t, 3H, CH_3).

8-*Formyloxy*-4-*phenyl*-1-*aza*-3-*thiabicyclo*[4.4.0]*decan*-2-*one* **25a**. (a) 3-(3-Butenyl)-4-ethoxy-6-phenyltetrahydro-1,3-thiazin-2-one (**15c**). 0.7 g (2.66 mmol) **11c** was reduced at −15° with 1.5 g (39.5 mmol) $NaBH_4$. Work-up afforded 0.6 g (77%) **15c** as a semi-solid mass; m.p. about 50°. IR ($CHCl_3$): 1620 cm^{-1} (CO); ^{1}H-NMR: 7.55–7.20 (m, 5H, Ph), 6.0–5.4 (m, 1H, C<u>H</u>=CH$_2$), 5.2–4.65 (m, 4H, CH=C<u>H</u>$_2$, NCHO and SCHPh), 4.1–2.95 (m, 4H, NCH$_2$ and OCH$_2$), 2.7–2.1 (m, 4H), 1.27 (t, 3H, CH_3).

(b) Cyclisation of **15c**. 0.2 g (0.60 mmol) **15c** was cyclised in 10 ml HCOOH for 4 days. Work-up afforded 0.151 g (76%) of a yellow oil, which solidified upon addition of EtOH; m.p. 128–131°. IR (KBr): 1715 cm^{-1} (ester CO); 1625 cm^{-1} (lactam CO); ^{1}H-NMR: 8.04 (s, 1H, OCHO), 7.50–7.25 (m, 5H, Ph), 5.25–4.80 (m, 2H, C<u>H</u>OCHO and NCH$_2$ eq) 4.59 (dd, 1H, SC<u>H</u>Ph), 3.75–3.40 (m, 1H, NCH bridgehead), 2.87–1.50 (m, 7H). An accurate mass determination gave 291.0919; $C_{15}H_{17}NO_3S$ requires 291.09289.

7-*Ethyl*-8-*formyloxy*-4-*phenyl*-1-*aza*-3-*thiabicyclo*[4.4.0]*decan*-2-*one* **25b**. (a) 3-(Z)-3-Hexenyl-4-hydroxy-6-phenyltetrahydro-1,3-thiazin-2-one (**15d**). 3.35 g (10.5 mmol) **11d** was reduced with 7.0 g (0.18 mol) $NaBH_4$ at −10°. After work-up, 3.5 g (95%) **15d** was obtained as a pale yellow oil. IR ($CHCl_3$): 1625 cm^{-1} (CO); ^{1}H-NMR: 7.5–7.2 (m, 5H, Ph), 5.80–5.25 (m, 2H, CH=CH), 5.05 (m, 1H, NCHO), 4.80 (m, 1H, SC<u>H</u>Ph), 4.1–3.2 (m, 4H, NCH$_2$ and OCH$_2$), 2.75–1.80 (m, 6H), 1.50–0.75 (m, 6H, 2 × CH_3).

(b) Cyclisation of **15d**, 0.2 g (0.63 mmol) in 10 ml formic acid for 3 days afforded 50 mg (25%) **25b** after work-up; m.p. 140° from EtOH. IR ($CHCl_3$): 1725 cm^{-1} (ester CO); 1620 cm^{-1}

(lactam CO); ^{1}H-NMR: 8.09 (s, 1H, OCHO), 7.37 (m, 5H, Ph), 5.20–4.70 (m, 2H, CHOCHO and NCH_2 eq), 4.46 (dd, 1H, SCHPh), 3.87–3.64 (ddd, 1H, NCH bridgehead), 2.93–2.27 (m, 3H), 2.05–1.40 (m, 5H), 1.04 (t, 3H, CH_3). An accurate mass determination gave 319.1228; $C_{17}H_{21}NO_3S$ requires 319.12419.

4,4 - *Dimethyl* - 1 - *aza* - 3 - *thiabicyclo*[4.4.0]*decane* -2,8 - *dione* **27**. (a) 3 - (3 - Butynyl) - 4 - ethoxy - 6,6 - dimethyltetrahydro - 1,3 - thiazin - 2 - one (**14e**). 3.9 g (18.5 mmol) **10e** was reduced with 7 g (0.18 mol) $NaBH_4$ at −10° to afford, after work-up, 3.8 g (86%) **14e** as a clear oil. IR ($CHCl_3$): 3310 cm^{-1} (C≡CH); 1615 cm^{-1} (CO); ^{1}H-NMR: 5.02 (m, 1H, NCHO); 4.20–3.35 (m, 4H, NCH_2 and OCH_2), 2.85–2.15 (m, 4H), 2.02 (m, 1H, C≡CH), 1.55 and 1.43 (s and s, 6H, 2 × CH_3), 1.22 (t, 3H, CH_3).

(b) Cyclisation of **14e**. 0.6 g (2.49 mmol) **14e** was dissolved in 10 ml formic acid and stirred in the dark at room temp for 7 days. Work-up afforded an oil, from which upon addition of dipe crystallised 270 mg **27**; m.p. 90–91°; yield 45%. IR ($CHCl_3$): 1720 cm^{-1} (ketone CO); 1620 cm^{-1} (lactam CO). ^{1}H-NMR: 4.87 and 4.65 (*d* of *t*, 1H, NCH_2 eq), 4.2–3.1 (m, 2H, NCH and NCH_2 ax), 2.75–2.4 (m, 4H), 2.12 and 1.99 (2s, 2H), 1.50 and 1.39 (s and s, 6H, 2 × CH_3). An accurate mass determination gave 213.0838; $C_{10}H_{15}NO_2S$ requires 213.08233.

4 - *Formyloxy* - 7 - (2 - *formyloxyethyl*) - 1 - *aza* - 8 - *thiabicyclo*[4.3.0]*nonan* - 9 - *one* **28**. (a) 3 - (3 - Butenyl) - 4 - hydroxy - 5 - (2 - hydroxyethyl) - thiazolidin - 2 - one (**22**). 2.7 g (11.1 mmol) **13** was reduced with 5.0 g (0.13 mol) $NaBH_4$ at −5°. Work-up afforded 1.1 g (46%) as an oil. IR ($CHCl_3$): 3360 cm^{-1} (OH); 1650 cm^{-1} (CO); the ^{1}H-NMR of the crude mixture showed no signal attributable to a methyl ester.

(b) 4 - (3 - Butenyl) - 6 - oxa - 2 - thia - 4 - azabicyclo[3.3.0]octan - 3 - one (**23a**). 0.5 g (2.3 mmol) **22** was dissolved in a mixture of 10 ml AcOH and 2 ml Ac_2O, and stirred at room temp for 22 hr. The solvent was then evaporated under reduced pressure, toluene added, the solvent removed *in vacuo* and this procedure repeated to give 0.45 g (99%) **23a** as an oil. IR ($CHCl_3$): 1670 cm^{-1} (CO); ^{1}H-NMR (250 MHz): 5.85–5.67 (m, 1H, CH=CH_2), 5.61 (d, 1H, NCHO), 5.15–5.0 (m, 2H, CH=CH_2), 4.19 (t, 1H, SCH), 4.05–3.82 (m, 2H, OCH_2), 3.58–3.28 (m, 2H, NCH_2), 2.45–2.0 (m, 4H). An accurate mass determination gave 199.0661; $C_9H_{13}NO_2S$ requires 199.0668.

(c) Cyclisation of **23a**. 0.3981 g of the above compound (2.0 mmol) was dissolved in formic acid (10 ml) and stirred overnight at 60°. Work-up and column chromatography afforded 0.2731 g (50%) **28** as a pale yellow oil. IR ($CHCl_3$): 1715 cm^{-1} (ester CO); 1670 cm^{-1} (lactam CO); ^{1}H-NMR: 8.09–8.02 (2s, 2H, 2 × OCHO), 5.20–4.85 (m, 1H, CHOCHO ring), 4.40–4.07 (m, 3H, CH_2OCHO and NCH_2 eq), 3.48 (m, 1H, NCH bridgehead), 2.81 (td, 1H, NCH_2 ax), 2.40–1.30 (m, 7H).

4 - (5 - *Hexenyl*) - 5 - *hydroxytetrahydro* - 1,4 - *oxazin* - 3 - *one* **14c**. Compound **10c**, 1.65 g (8.5 mmol) was reduced with 3.2 g (84.3 mmol) $NaBH_4$ at −20°. Work-up afforded 0.985 g (59%) **14c** as a solid; m.p. 55–58° (from dipe). IR ($CHCl_3$): 3370 cm^{-1} (OH); 3330 cm^{-1} (C≡CH); 1665 cm^{-1} (CO); ^{1}H-NMR: 4.76 (m, 1H, sharpened with D_2O; CHOH), 4.15 (m, 2H, OCH_2CO), 4.05–3.15 (m, 5H; 4H upon addition of D_2O; NCH_2 and OCH_2COH), 2.23 (m, 2H, CH_2C≡C), 1.97 (t, 1H, C≡CH), 1.85–1.35 (m, 4H). An accurate mass determination gave 197.1051; $C_{10}H_{15}NO_3$ requires 197.10517.

7 - *Ethyl* - 8 - *formyloxy* - 1 - *aza* - 4 - *oxabicyclo*[4.4.0]*decan* - 2 - *one* **31a**. (a) 4 - (Z) - 3 - Hexenyl - 5 - hydroxytetrahydro - 1,4 - oxazin - 3 - one (**15b**). 1.58 g (8.0 mmol) **11b** was reduced with 2.87 g (75.6 mmol) $NaBH_4$ at −15°. Work-up afforded 1.48 g (94%) **15b** as a low melting solid. IR ($CHCl_3$): 3380 cm^{-1} (OH); 1655 cm^{-1} (CO); ^{1}H-NMR: 5.67–5.15 (m, 2H, CH=CH), 4.76 (m, 1H, sharpened with D_2O; CHOH), 4.15 (m, 2H, OCH_2CO), 4.05–3.15 (m, 5H; 4H with D_2O; NCH_2 and OCH_2COH), 2.55–1.87 (m, 4H), 0.96 (t, 3H, CH_3). An accurate mass determination gave 199.1220; $C_{10}H_{17}NO_3$ requires 199.12082.

(b) Cyclisation of **15b**. 0.3 g (1.51 mmol) **18b** was dissolved in 50 ml HCOOH and stirred at room temp for 19 hr. Work-up afforded 0.34 g **31a** as a clear oil (quantitative yield). IR ($CHCl_3$): 1725 cm^{-1} (ester CO); 1655 cm^{-1} (lactam CO); ^{1}H-NMR: 8.09 (s, 1H, OCHO), 5.20–4.93 (m, 1H, CHOCHO), 4.76 (dm, 1H, NCH_2 eq), 4.16 (s, 2H, OCH_2CO), 4.1–3.7 (m, 2H, OCH_2CN), 3.49 (m, 1H, NCH bridgehead), 2.84–2.49 (m, 1H, NCH_2 ax), 2.1–1.4 (m, 5H), 1.02 (t, 3H, CH_3). This compound was further characterised by saponification to **31b**.

7 - *Ethyl* - 8 - *hydroxy* - 1 - *aza* - 4 - *oxabicyclo*[4.4.0]*decan* - 2 - *one* **31b**. Compound **31a** 0.94 g (0.41 mmol) was dissolved in 5 ml MeOH, 0.05 g (1 pill) of solid NaOH added and stirred at room temp for 2 hr. The mixture was quenched with 1 ml AcOH, the soln stirred for an additional 30 min, the solvent removed under reduced pressure, the residue taken up in ethyl acetate and filtered over a short column (silica). Removal of the solvent *in vacuo* afforded **31b** as a crystalline mass (0.80 g, 97%); m.p. 122–124 (dipe). IR ($CHCl_3$): 3410 cm^{-1} (OH); 1640 cm^{-1} (CO); ^{1}H-NMR (250 MHz): 4.66 (ddd, 1H, CHOH), 4.11 (d, 2H, OCH_2CO), 4.98–4.78 (m, 3H, NCH_2 eq and OCH_2CN), 3.38 (m, 1H, NCH bridgehead), 2.55 (td, 1H, NCH_2 ax), 2.0–1.3 (m, 6H), 1.01 (t, 3H, CH_3). An accurate mass determination gave 199.1193; $C_{10}H_{17}NO_3$ requires 199.12082.

11 - *Formyloxy* - 7 - *aza* - 4 - *oxatricyclo*[7.3.1.0^{2,7}]*tridecan* - 6 - *one* **32**. (a) 4 - (3 - Cyclohexenylmethyl) - 5 - hydroxytetrahydro - 1,4 - oxazin - 3 - one (**16b**). 1.0 g (4.8 mmol) **12b** was reduced with 2.0 g (52.7 mmol) $NaBH_4$ at −25° to afford 0.93 g (92%) of **16b** as a viscous oil. IR ($CHCl_3$): 3420 cm^{-1} (OH); 1660 cm^{-1} (CO); ^{1}H-NMR: 6.67 (m, 2H, CH=CH), 4.78 (m, 1H, sharpens with D_2O; CHOH), 4.16 (d, 2H, OCH_2CO), 3.87 (m, 2H, OCH_2), 3.8–2.6 (m, 3H, changes to 2H with D_2O; NCH_2 and OH), 2.3–1.1 (m, 7H). An accurate mass determination gave 211.1221; $C_{11}H_{17}NO_3$ requires 211.12082.

(b) Cyclisation of **16b**. 0.3609 g (1.71 mmol) **16b** was dissolved in 15 ml HCOOH and stirred at room temp for 19 hr. Work-up afforded 0.2913 g of an oil which solidified upon addition of dipe; m.p. 136–138° yield 71%. IR ($CHCl_3$): 1715 cm^{-1} (ester CO); 1640 cm^{-1} (lactam CO); ^{1}H-NMR: 7.99 (s, 1H, OCHO), 5.55–5.15 (m, 1H, CHOCHO), 4.69–4.48 (dm, 1H, NCH_2 eq), 4.23 (s, 2H, OCH_2CO), 4.0–3.55 (m, 3H, OCH_2CHN), 3.0–3.75 (dm, 1H, NCH_2 ax), 2.5–1.3 (m, 8H). An accurate mass determination gave 239.1140; $C_{12}H_{17}NO_4$ requires 239.11573.

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