Ring contraction of dihydro[1,3]thiazines to pyrroles on cyclisation[1]

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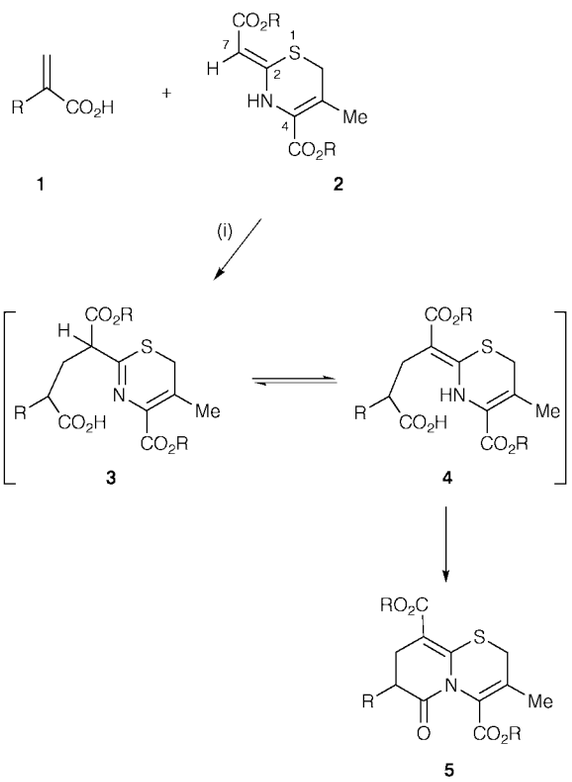
Dihydrothiazines such as **8** and **12**, which are disubstituted at C-7, undergo an interesting cyclisation–ring contraction reaction with substituted acrylic acids yielding the pyrroles **9** and **13** respectively. This contrasts with the corresponding reaction of thiazines **2** which are monosubstituted at C-7 which undergo a simple cyclisation reaction. A mechanism is suggested for the cyclisation–ring contraction process.

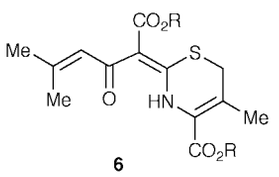
During our studies on the synthesis of bicyclic pyridone and dihydropyridone analogues of β-lactam antibiotics, we discovered that 1,3-thiazines of the type **2** could be cyclised by reaction with a variety of substituted acylaminoacrylic acids **1** to yield bicyclic products **5**[2] as shown in Scheme 1. The mechanism for this reaction, suggested in Scheme 1, involves

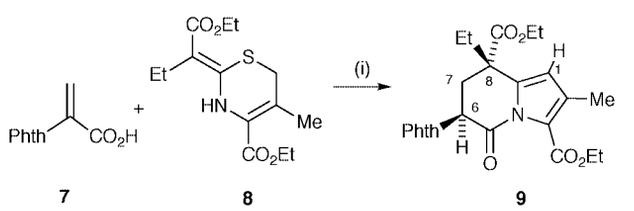


Scheme 1 *Reagents and conditions*: (i) PCl_3/benzene/dioxane/Δ.

Michael attack on the acylaminoacrylic acid **1** by the enamine moiety of the thiazine **2** to yield the imine **3** which, on rearrangement to the enamine **4**, cyclises to form the bicyclic product **5**. When 3,3-dimethylacrylic acid was used in the reaction, steric hindrance at the β-position blocked the Michael reaction and the acylated thiazine **6** was obtained.[2]

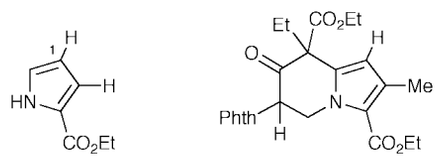
Since there would be no possibility of imine–enamine tautomerism corresponding to **3**→**4** if the enamine moiety of the thiazine had no hydrogen at position 7, as is the case in compound **8**, subsequent cyclisation to give products corresponding to **6** would appear to be precluded. It was, therefore, of interest to investigate the reaction of "blocked" thiazine enamines such as **8**[3] with substituted acrylic acids. We therefore reacted phthalimidoacrylic acid **7**[4] with the thiazine **8** in the presence of phosphorus trichloride (Scheme 2). The product,





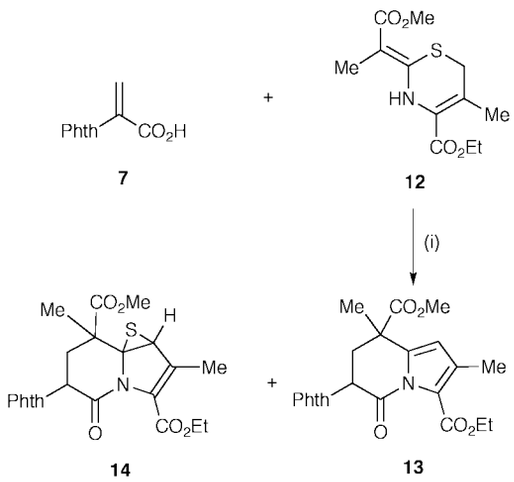
Scheme 2 *Reagents and conditions*: (i) PCl_3/benzene/dioxane/Δ. Phth = phthalimido.

$C_{25}H_{26}N_2O_7$, appeared to be a single diastereoisomer with spectral data in accord with its assignment as the pyrrole **9**. The ^{1}H NMR spectrum showed absorptions for the phthalimido aromatic protons and the two ethyl ester groups, one of which was an ABX_3 system and one a A_2X_3 system. There were also absorptions due to the vinyl methyl singlet at δ 2.19 ppm and the C-8 ethyl group that appeared as an ABX_3 system at δ 0.94 ppm (3H) and δ 1.92 and 2.36 ppm (2H, J_{AB} 14 and $J_{Me,H}$ 7.4 Hz). The three dihydropyridone protons, H-6 and H-7, appeared as an ABX system at δ 2.61, 2.86 and 5.68 ppm (J_{AB} 12, J_{AX} 5.2 and J_{BX} 12.8 Hz) and there was a singlet at δ 6.14 ppm which correlated well with the β-proton of pyrrole **10** at δ 6.1 ppm.[5] Assignments were confirmed by decoupling experiments and the ^{13}C NMR spectrum had four carbonyl absorptions for conjugated ester (δ 162 ppm), amide (δ 163.27 ppm), phthalimide



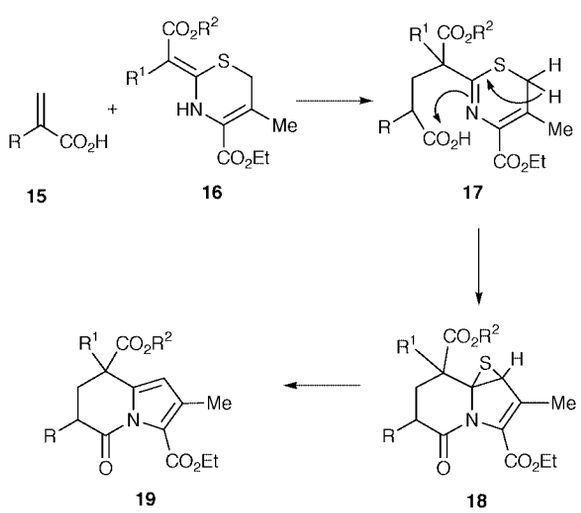
(δ 167.03 ppm) and ester (δ 172.01 ppm), ruling out the alternative ketone structure **11**. We were unable to assign the relative stereochemistry from the spectral data and have suggested the stereochemistry in structure **9** as being likely to be the more thermodynamically stable of the two possible diastereoisomers.

When the thiazine **12** was reacted with phthalimidoacrylic acid **7** under identical conditions to those used above, a mixture of two products was obtained (Scheme 3). One of these had



Scheme 3 *Reagents and conditions*: (i) PCl_3/benzene/dioxane/Δ.

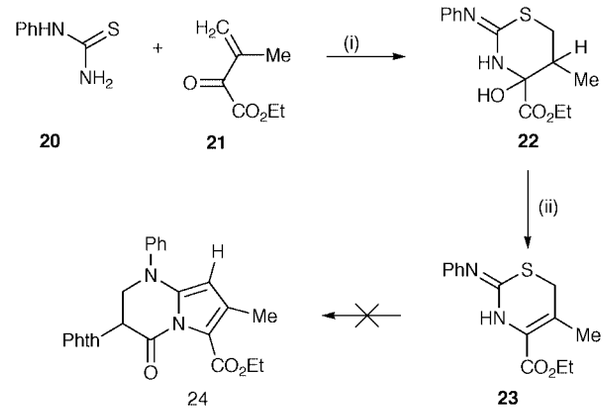
analytical and spectral data analogous to those of the product **9** from the previous reaction and so this product was assigned the structure **13**. The second product, $C_{23}H_{22}N_2O_7S$, isolated in 10% yield, appeared to be a mixture of two diastereoisomers of the episulfide **14**, the episulfide proton in the diastereoisomers being two singlets at δ 3.44 and 3.55 ppm. This suggested the mechanism shown in Scheme 4 for the ring contraction. The



Scheme 4

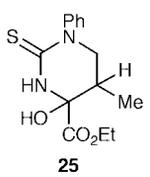
first step would be Michael attack of the enamine **16** on the acrylamide **15** to give the intermediate **17**, analogous to the first step in the mechanism suggested in Scheme 1 for the corresponding reaction of the unsubstituted thiazine **2**. Rearrangement to an enamine analogous to **4** now being precluded, it would appear that the cyclisation–rearrangement **17**→**18** has occurred to give the episulfide **18** which eliminates sulfur yielding the aromatic pyrrole **19**.

Having discovered an interesting ring contraction–cyclisation reaction, it was of interest to see if this reaction might occur when a monosubstituted nitrogen replaced the disubstituted carbon at C-7 of the thiazine. The hydrochloride of the thiazine **22** was therefore prepared as an unstable oil by reaction of



Scheme 5 *Reagents and conditions*: (i) HCl/dioxane; (ii) PTSA/DME/Δ.

N-phenylthiourea **20** with ethyl 3-methyl-2-oxobut-3-enoate **21**[6] in HCl–dioxane (Scheme 5). The oil was difficult to purify but, on dehydration using toluene-*p*-sulfonic acid, the hydrochloride of the thiazine **23** was obtained. The spectra were in keeping with the structure **23** rather than that of the alternative thiourea **25**. This latter compound would be unlikely to occur



as a hydrochloride salt. The dihydrothiazine **23** proved to be unstable to the acidic coupling conditions used in preparing the pyrroles **9** and **19** and when a coupling was attempted using DCCD, no product corresponding to the pyrrole **24** could be isolated.

Experimental

Melting points were determined on a Kofler hot stage and are uncorrected. Ultra-violet spectra were recorded on a PyeUnicam SP800 spectrophotometer. Infra-red spectra were recorded on Perkin-Elmer 257 and 477 spectrometers with calibration on the polystyrene 1603 cm^{-1} band. ^{1}H-NMR spectra were recorded on Perkin-Elmer R32 (90 MHz) and JEOL EM360 (60 MHz) spectrometers. 220 MHz ^{1}H-NMR spectra were recorded by the Physico-Chemical Measurements Unit, Harwell and 100 MHz ^{1}H-NMR spectra were obtained by courtesy of the Agricultural Research Council Unit of Nitrogen Fixation, Sussex. ^{13}C-NMR spectra were recorded on a JEOL EC-100 (25.1 MHz) Fourier transform spectrometer. Tetramethylsilane was used as an internal standard whenever possible. Other ^{1}H- and ^{13}C- NMR spectra were recorded by Mr B. Wright and Mr H. Beeley, Zeneca Pharmaceuticals, Alderley Park, Cheshire. *J* values are given in Hz. Mass spectra were recorded on an AEI-MS 30 spectrometer used in conjunction with an AW-DS 50 computer for accurate mass measurement by Mrs M. Vickers at Zeneca Pharmaceuticals, Alderley Park, Cheshire. C, H and N microanalyses were carried out at The University of Sussex by Mr and Mrs A. G. Olney, and O and S values were obtained from H. Malissa and G. Reuter Laboratorien, Elbach, Germany. Thin layer chromatography was carried out using Kieselgel GF 254 from E. Merck of thickness 0.25 mm (analytical) and 0.75 mm (preparative).

Diethyl 8-ethyl-2-methyl-5-oxo-6-phthalimido-5,6,7,8-tetrahydroindolizine-3,8-dicarboxylate (9)

Phosphorus trichloride (46 mg, 0.335 mmol), α-phthalimido-

acrylic acid (**7**)[3] (70 mg, 0.323 mmol) and ethyl 3,6-dihydro-2-(1-ethoxycarbonylpropylidene)-5-methyl-2*H*-1,3-thiazine-4-carboxylate (**8**)[2] (100 mg, 0.334 mmol) were heated to reflux under nitrogen in dioxane (2 ml) and benzene (1 ml). After 10 h the solvent was removed *in vacuo* and the yellow foam was dissolved in ethyl acetate (10 ml), washed with saturated aqueous sodium hydrogen carbonate (5 ml) and 1 M hydrochloric acid (5 ml) and dried ($MgSO_4$). Removal of the solvent *in vacuo* gave an oil (140 mg) which was subjected to thin layer chromatography on silica gel eluting with $CHCl_3$. Diethyl 8-ethyl-2-methyl-5-oxo-6-phthalimido-5,6,7,8-tetrahydroindolizine-3,8-dicarboxylate (**9**) was obtained as a colourless oil (85 mg, 54%) which was crystallised from dichloromethane and diethyl ether (46 mg, 30%) (Found C, 63.5; H, 5.6; N, 5.9. $C_{25}H_{26}N_2O_7$ requires C, 64.4; H, 5.6; N, 6.0%); *m*/*z* (EI) 466 ($[M]^+$); λ_{max}(MeOH)/nm 231, 240, 250, 275 and 288 (sh) (ε/dm^3 mol^{-1} cm^{-1} 11100, 8990, 6180, 4440 and 3540); ν_{max}(film)/cm^{-1} 1785 (sh) (phthalimido), 1750–1710 (broad, amide and ester), 1600 and 1515 (pyrrole); δ_H (220 MHz, C^2HCl_3) 0.94 (3H, t, *J* 7.4, CH_3), 1.26 and 1.31 (2 × 3H, 2 × t, 2 × *J* 7, 2 × CH_3), 1.92 and 2.36 (2 × 1H, 2 × dq, J_{AB} 14, $J_{Me,H}$ 7.4, CH_2), 2.61 (1H, dd, $J_{7A,7B}$ 12, $J_{7A,6}$ 5.2, H-7A), 2.86 (1H t, $J_{7B,7A}$ 12, $J_{7B,6}$ 12.8, H-7B), 4.27 (2H, q, *J* 7.0, CH_2O), 4.24 and 4.30 (2H, qq, *J* 7.0, J_{AB} 10.8, CH_2O), 5.68 (1H, dd, $J_{6,7B}$ 12.8, $J_{6,7A}$ 5.2, H-6), 6.14 (1H, s, pyrrole CH) and 7.8 (4H, Ar*H*). Decoupling experiments showed that when the resonance at δ 5.68 ppm was irradiated then the dd at δ 2.61 and 2.86 ppm collapsed to an AB system. Similarly irradiation at δ 0.94 ppm caused the two dq at δ 1.92 and 2.36 ppm to collapse to an AB system; δ_C (25.15 MHz, C^2HCl_3) 8.62 (CH_3), 11.82 (MeC=), 14.08 (Me), 32.22 and 32.82 (2 × CH_2), 46.90 (C), 49.14 (CN), 61.10 and 62.13, 2 × CH_2O), 113.88 (Ar), 121.89 (Ar), 131.11 (Ar), 131.84 (Ar), 134.27 (Ar), 136.69 (pyrrole), 162.00 (ester), 163.27 (amide C=O), 167.03 (phthalimido C=O) and 172.01 (ester C=O).

Methyl ethyl 2,8-dimethyl-5-oxo-6-phthalimido-5,6,7,8-tetrahydroindolizine-3,8-dicarboxylate (13) and methyl ethyl 2,8-dimethyl-1,8*a*-epithio-1,5,6,7,8,8*a*-hexahydro-5-oxo-6-phthalimidoindolizine-3,8-dicarboxylate (14)

2-Phthalimidoacrylic acid **7** (400 mg, 1.84 mmol), phosphorus trichloride (256 mg, 1.86 mmol) and ethyl 3,6-dihydro-2-(1-methoxycarbonylethylidene)-5-methyl-2*H*-1,3-thiazine-4-carboxylate **12** (500 mg, 1.85 mmol) were heated to reflux under nitrogen in dioxane (4 ml) and benzene (1 ml). After 5 h, TLC showed that no thiazine remained. The solvent was removed *in vacuo* and the residue was dissolved in ethyl acetate (25 ml) and washed successively with saturated aqueous sodium hydrogen carbonate (10 ml), 1 M hydrochloric acid (10 ml) and saturated aqueous sodium chloride (10 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo* to give a colourless oil (630 mg). Preparative TLC gave two main fractions. The first (230 mg, 28%) was shown to be methyl ethyl 2,8-dimethyl-5-oxo-6-phthalimido-5,6,7,8-tetrahydroindolizine-3,8-dicarboxylate (**13**) and was crystallised from dichloromethane and diethyl ether (93 mg, 11.5%); mp 155–157 °C (Found C, 62.9; H, 5.2; N, 6.3. $C_{23}H_{22}N_2O_7$ requires C, 63.0; H, 5.1; N, 6.4%); *m*/*z* (EI) 438 ($[M]^+$), λ_{max} (MeOH)/nm 232, 240, 250 and 287; ν_{max} (CCl_4)/cm^{-1} 1780 (phthalimido), 1730 (sh, ester), 1720 (unsaturated ester), 1715 (sh, phthalimido), 1690 (amide); δ_H (100 MHz, C^2HCl_3) 1.27 (3H, t, *J* 7.5, CH_3), 1.69 (3H, s, CH_3), 2.18 (3H, s, CH_3-C=), 2.50 (1H, dd, $J_{7A,7B}$ 13, $J_{7A,6}$ 5.5, H-7A), 2.94, (1H, t, $J_{7B,7A} = J_{7B,6} = 13$, H-7B), 3.78 (3H, s, OCH_3), 4.26 (2H q, *J* 7.5, CH_2O), 5.54 (1H, dd, $J_{7B,6}$ 13, $J_{7A,6}$ 5.5, H-6), 6.08 (1H, s, H-1) and 7.8 (4H, m, ArH).

The second compound from the column was assigned as methyl ethyl 2,8-dimethyl-1,8*a*-epithio-1,5,6,7,8,8*a*-hexahydro-5-oxo-6-phthalimidoindolizine-3,8-dicarboxylate (**14**) (85 mg, 10%) and was crystallised from dichloromethane and diethyl ether (22 mg, 3%); mp 148–149 °C; λ_{max} (MeOH)/nm 239 (sh) and 293 (Found C, 58.0; H, 4.8; N, 5.8. $C_{23}H_{22}N_2O_7S$ requires C, 58.7; H, 4.7; N, 5.95%); (*m*/*z* (EI) $[M]^+$ found 470.113423. $C_{23}H_{22}N_2O_7S$ requires *M* 470.114761); δ_H (60 MHz, C^2HCl_3) 1.20 (3H, t, *J* 7.5, CH_3), 1.60 and 1.73 (>3H, 2s, diastereoisomeric CH_3C), 2.12 (3H, s, CH_3-C=), 2.43 (1H, dd, $J_{7A,7B}$ 13, $J_{7A,6}$ 6, H-7A), 3.00 (1H, t, $J_{7B,7A} = J_{7B,6}$ 13, H-7B), 3.44 and 3.55 (1H, 2s, diastereoisomeric CHS), 3.80 (3H, s, CH_3O), 4.30 (2H, q, *J* 7.5, CH_2O), 5.43 (1H, dd, $J_{6,7B}$ 13, $J_{7A,6}$ 6, H-6) and 7.8 (4H, m, ArH).

Ethy1 4-hydroxy-5-methyl-2-phenylimino-1,3-thiazinane-4-carboxylate hydrochloride 22

N-Phenylthiourea (**20**) (1.91 g, 12.6 mmol) and ethyl 3-methyl-2-oxobut-3-enoate (**21**)[6] (3.5 g, *ca*. 80% pure by ^{1}H-NMR spectroscopy, 19.7 mmol) were dissolved in dioxane (20 ml), saturated at 0 °C with dry hydrogen chloride and allowed to stand at room temperature for 2 days. The solvent was removed *in vacuo* to give a fairly pure oil (4.5 g) which could not be purified by crystallisation or by chromatography without decomposition (4.5 g, impure); ν_{max} ($CHCl_3$)/cm^{-1} 1730 (ester), 1590 (conjugated C=N); δ_H (90 MHz, C^2HCl_3) 1.03 and 1.08 (3H, 2d, 2 × *J* 7, CH_3), 1.36 (3H, t, *J* 7, CH_3), 3.6 (1H, complex m, CH), 3.2 to 4.2 (2H, m, diastereoisomeric CH_2S), 4.33 (2H, q, *J* 7, CH_2O), 4.4 (1H br s, OH, exchanges with ^2H_2O), 7.34 (5H, s, ArH) and 7.45 (2H, m, NH_2, exchanges with ^2H_2O).

Ethyl 3,6-dihydro-5-methyl-2-phenylimino-2*H*-1,3-thiazine-4-carboxylate hydrochloride 23

The crude 4-hydroxy-5-methyl-2-phenylimino-4*H*-1,3-thiazinane-4-carboxylate hydrochloride (**22**) (1.4 g) was dissolved in dimethoxyethane (20 ml). Toluene-*p*-sulfonic acid (50 mg) was added and the solution was heated to 50–70 °C for 2.5 h and left to stand over 3 days when a white solid precipitated. The solid, which was found to decompose on silica gel, was filtered off and recrystallised from dichloromethane and petroleum ether to give white needles (950 mg, 72%); mp 135–145 °C (decomp.) (Found C, 53.6; H, 5.3; N, 8.6; O, 10.1; S, 10.1. $C_{14}H_{17}N_2O_2SCl$ requires C, 53.75; H, 5.5; N, 8.95; O, 10.2; S, 10.25%); *m*/*z* (EI) 276 ($[M - HCl]^+$); λ_{max} (MeOH)/nm 267 and 302 (ε/dm^3 mol^{-1} cm^{-1} 7122 and 7482); ν_{max} (KBr)/cm^{-1} 1725 (unsaturated ester), 1655 (C=C); δ_H (60 MHz, C^2HCl_3) 1.45 (3H, t, *J* 7, CH_3), 2.40 (3H, CH_3-C=), 3.58 (2H, s, CH_2S), 4.42 (2H, q, *J* 7, CH_2O), 7.37 (5H, m, ArH), *ca.* 12.2 (2H, br s, NH_2, exchanges with ^2H_2O); δ_C (25.15 MHz, C^2HCl_3) 14.26 (CH_3), 19.66 (CH_3-C=), 31.31 (CS), 62.73 (CH_2O), 124.62 and 126.68 (2 × C=), 125.10, 128.74 and 129.47 (Ar), 134.93 (Ar), 160.30 (N=C-S) and 167.03 (ester).

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References

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