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Reductive and Catalytic Rearrangements of 2-Vinyl-1,3-Thiazetidines[1]

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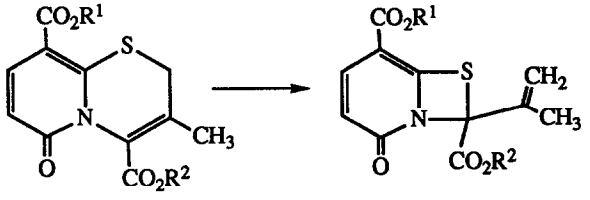
Abstract 2-Vinyl-1,3-thiazetidines have been shown to undergo a novel rearrangement to give thiazolidines such as **3** in good yield on hydrogenation using heterogeneous catalysts. When homogeneous catalysts are used, rearrangement takes a different course and thiazines such as **1** are formed. Borohydride reduction yields thiolactols such as **20**.

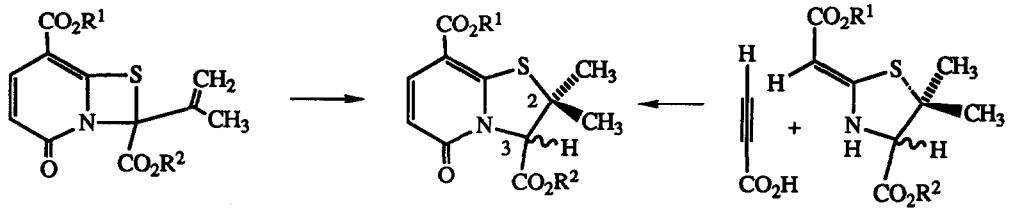
In work related to the synthesis of strained β-lactam systems, we discovered a novel and high yielding route to 2-vinyl-1,3-thiazetidines such as compound **2**, using photochemical rearrangement of 1,3-thiazines such as **1**.[3] Having gained access to this interesting system, we have investigated its reactivity and now report some novel catalytic and reductive rearrangements undergone by this system.



(1) **(2)**

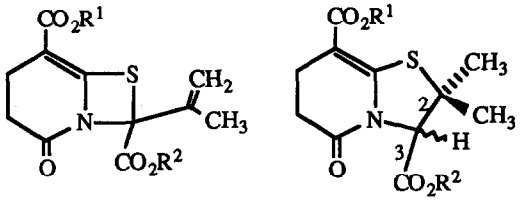
Hydrogenation of the thiazetidine (**2**, $R^1 = R^2 = Et$)[3] at room temperature and pressure using Adams catalyst and either ethyl acetate or ethanol as solvent gave a product $C_{15}H_{19}NO_5S$ in 96% yield. The presence of two distinct quaternary methyl groups and a single uncoupled proton in the ^{1}H-NMR spectrum, in addition to the two doublets due to the pyridone α- and β-hydrogens, suggested that hydrogenation had been accompanied by

rearrangement to give the fused thiazolidine (**3**, $R^1 = R^2 = Et$). This was confirmed by an unambiguous total synthesis of the compound by reacting the thiazolidine (**5**, $R^1 = R^2 = Et$) with propiolic acid **4** and DCCD.[4]



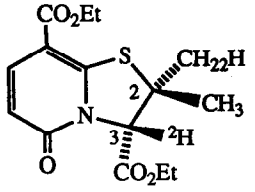
(2) **(3)** **(4)** **(5)**

When the dihydropyridone-thiazetidine (**6**, $R^1 = R^2 = Et$)[3] was hydrogenated under the above conditions, the corresponding dihydropyridone-thiazolidine (**7**, $R^1 = R^2 = Et$) was obtained in 60% yield. The structure of this compound was confirmed by an independent synthesis in which the thiazolidine (**5**, $R^1 = R^2 = Et$)[4] was reacted with acrylic acid and DCCD.



(6) **(7)**

In order to assess the mechanism of the reaction, its stereospecificity was investigated. Relative stereochemistry could be assigned to the absorptions in the ^{1}H-NMR spectrum due to the two thiazolidine methyl groups in (**3**, $R^1 = R^2 = Et$), using nOe measurements. Irradiation of the lower field methyl signal caused a 30% enhancement in the singlet due to the proton H-3, whereas irradiation of the higher field methyl signal gave a 5% enhancement to this signal. The upper field signal therefore represented that methyl group which was *anti* to the proton at C-3. The thiazetidine (**2**, $R^1 = R^2 = Et$) was now subjected to the hydrogenolytic rearrangement reaction using deuterium gas in place of hydrogen and either EtO^2H or ethyl acetate as solvent. The product was evidently dideuteriated from the mass spectrum but the NMR spectra indicated that it consisted of a mixture of the products **8** and **9**. In the ^{1}H-NMR spectrum, each of the absorptions due to the 2α- and 2β-methyl groups was accompanied by a second $C^1H_2{}^2H$ singlet to higher field. Both methyl singlets in the proton-decoupled ^{13}C-NMR spectrum were also accompanied by a triplet to slightly higher field. Deuteriation was non-stereospecific but, although the results varied slightly over a number of experiments, there was always greater incorporation of deuterium into the methyl group, which was *anti* to the C-2 hydrogen. There was, on average, an approximately 2:1 preference for *anti* addition of hydrogen in the rearrangement. Catalytic deuteriation using 10% palladium on charcoal catalyst proved to be almost entirely non-stereospecific.



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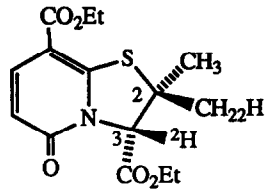
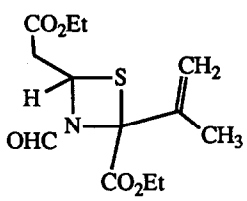


(9)

When hydrogenation of the thiazetidine (**2**, $R^1 = R^2 = Et$) was conducted using tris(triphenylphosphine) rhodium(I) chloride, a product was obtained in 73% yield. This proved to have identical spectroscopic and physical properties to an authentic sample of the thiazine (**1**, $R^1 = R^2 = Et$).[4] Since there was no change in oxidation level in this reaction, it was evident that hydrogen was unnecessary for the rearrangement, and indeed, the rearrangement was shown to occur equally well when the reaction was conducted in an atmosphere of argon. Although reduction of the monocyclic thiazetidine **10**[3] with Adams catalyst gave no recognisable products, reaction of this compound with tris(triphenylphosphine)rhodium chloride gave the thiazine **11**, spectroscopically identical with an authentic sample [3], albeit in low yield.



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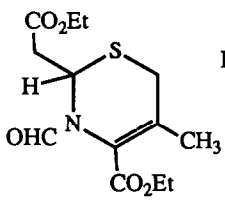

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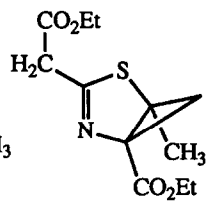

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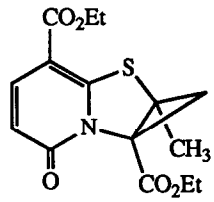
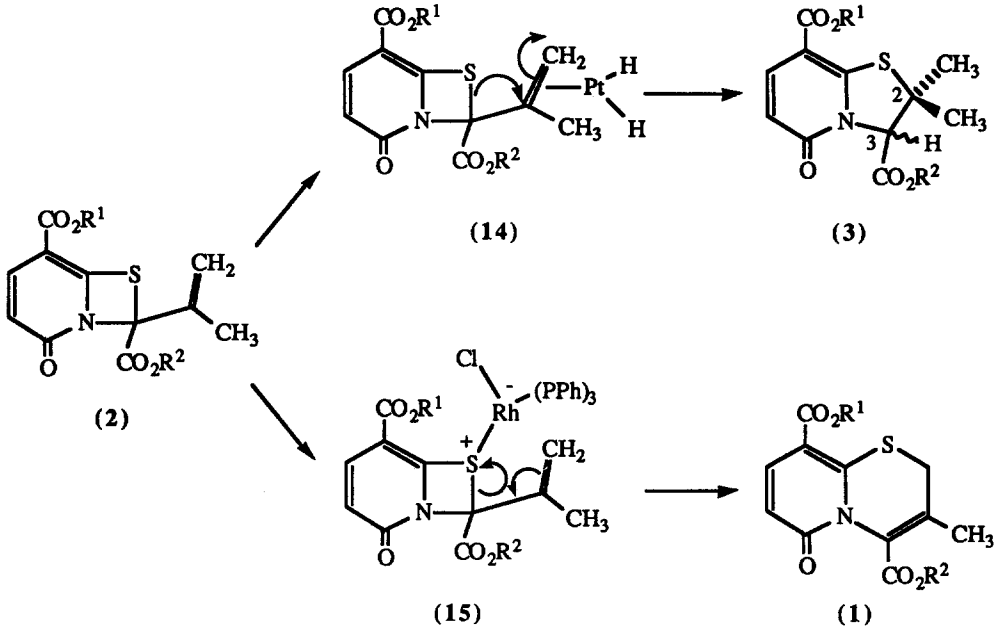


(13)

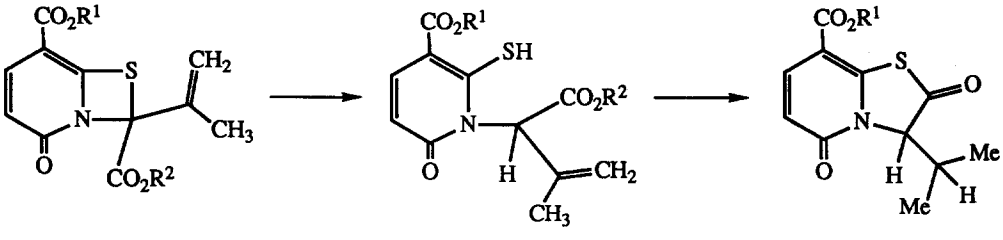
Treatment with a homogeneous catalyst had evidently led to an entirely different rearrangement from that found using the heterogeneous catalysts platinum and palladium. The possible intermediacy of the tricyclic intermediate **13** in the rearrangement was ruled out by synthesis of this compound by reaction of the cyclopropylthiazoline **12** [5] with propiolic acid. When the tricyclic compound **13** was reacted under the catalytic reduction conditions, it was recovered unchanged.

A possible explanation for the dichotomy observed between the heterogeneous and homogeneous reactions is shown in the scheme below. Pt(II) has a known tendency to complex with olefinic bonds, so that a species **14** might be formed. This would trigger the movement of electrons to the olefin and so 1,2-shift of sulphur as shown followed by addition of hydrogen at C-2 would lead eventually to the thiazolidine **3**. The "softer" Rh(I) would be expected to have a greater tendency to complex with sulphur yielding the intermediate **15**. Movement of electrons would now be directed to the sulphur and away from the olefin as shown, and this would lead to rearrangement to the thiazine **1** as shown.



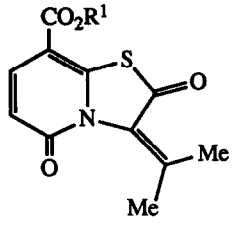
(2) (14) (3) (15) (1)

On one occasion, hydrogenation of the thiazetidine (**2**, $R^1 = R^2 = Et$), using Adams catalyst gave a second product in addition to the thiazolidine (**3**, $R^1 = R^2 = Et$). This had spectral data in accord with the thiolactone structure (**17**, $R^1 = Et$). Hydrogenation of the thiazetidine (**2**, $R^1 = PhCH_2$, $R^2 = Me$) using Adams catalyst, was not accompanied by debenzylation and gave a greater proportion of the thiolactone (**17**, $R^1 = PhCH_2$) to the thiazolidine (**3**, $R^1 = PhCH_2$, $R^2 = Me$) than had been obtained from the diethyl ester. The thiolactones **17** would result from hydrogenolysis of the sulphur carbon bond of the thiazetidines to give an intermediate such as **16** which on thiolactonisation and reduction of the olefin would yield the thiolactone.



(2) (16) (17)

Results from hydrogenolysis of the thiazetidine (**2**, $R^1 = PhCH_2$, $R^2 = Me$) using 5% rhodium on alumina as catalyst, indicated that hydrogenolysis of the sulphur carbon bond was likely to be the first step in the process, since this reaction gave, in addition to 19% of the thiazolidine (**3**, $R^1 = PhCH_2$, $R^2 = Me$), the isopropylidene thiolactones (**18**, $R^1 = PhCH_2$, $R^2 = Me$) in 32% yield and (**19**, $R^1 = PhCH_2$, R = Me) in 10% yield.



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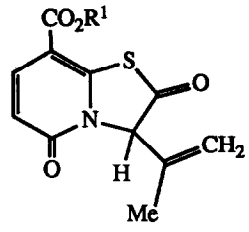
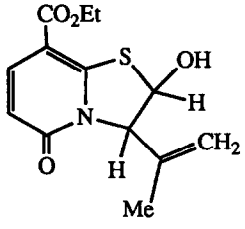


(19)

A possible explanation for the fact that thiazolidine formation is more likely to occur when the diethyl ester (2, $R^1 = R^2 = Et$) is hydrogenolysed, whereas thiolactone formation predominates when the benzyl methyl diester (2, $R^1 = PhCH_2$, $R^2 = Me$) is hydrogenolysed, is the steric effect of the C-3 ester group. A more bulky ester might prevent thiolactonisation and therefore encourage thiazolidine formation. The difference here is simply the difference between an ethyl ester and a methyl ester. To investigate the relevance of this factor, we prepared the thiazetidine benzyl ethyl diester (2, $R^1 = PhCH_2$, $R^2 = Et$) by photolysis of the pyridothiazine (1, $R^1 = PhCH_2$, $R^2 = Et$). Hydrogenolysis of this compound gave nearly equal amounts of the thiolactone (17, $R^1 = PhCH_2$) and the thiazolidine (3, $R^1 = PhCH_2$, $R^2 = Et$). The bulk of the C-3 ester therefore seems to have little effect on the outcome of the reaction and it may be that the pyridone ester group exerts some effect, forcing the bulky complexed olefin away from the sulphur, so that thiolactonisation might be the more likely process to occur.

In an attempt to direct the reaction entirely towards formation of a thiazolidine 3, we hydrolysed the diester (2, $R^1 = R^2 = Et$) to the diacid (2, $R^1 = R^2 = H$). Since the salt of the acid should be incapable of thiolactone formation, we subjected the potassium salt to the hydrogenolytic conditions. No thiolactone was obtained and the thiazolidine (3, $R^1 = R^2 = H$) was the only product, although the yield was low. Hydrogenolysis of the diacid itself gave only thiolactone (17, $R^1 = H$) as product, again in low yield.

On investigation of the reaction of other reducing agents on the labile vinylthiazetidine system, we reacted the thiazetidine (2, $R^1 = R^2 = Et$) with sodium borohydride in aqueous tetrahydrofuran. We obtained a product $C_{13}H_{15}NO_4S$ in 70% yield. This had evidently CHOH and isopropenyl functions from its spectra and the thiolactol structure 20 fitted the spectroscopic and analytical data. When the reaction was repeated using NaB^2H_4 in THF / ^2H_2O, the dideuterio analogue 21 was obtained, the ^{13}C spectrum of which showed that two carbon atoms (δ 75.12 and 80.68) were deuteriated. The structure was finally proved by catalytic reduction to the thiolactol 22, which we obtained independently by reduction of the thiolactone (17, $R^1 = Et$) previously prepared by the hydrogenolytic rearrangement.



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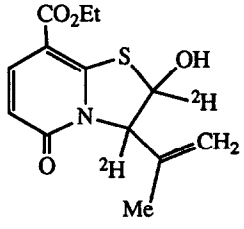

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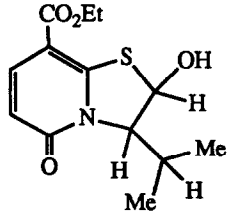

(22)

A possible mechanism for the formation of the thiolactol **20** would be reductive opening of the thiazetidine ring to a thiol, which would then cyclise to a thiolactone. This in turn would be further reduced to the thiolactol.

EXPERIMENTAL

Mps were determined on a Kofler hot-stage apparatus, IR spectra were recorded on Perkin Elmer 157G, 577, and PE1710 instruments and UV spectra on Pye-Unicam SP800 and Phillips PU8720 spectrophotometers. ^{1}H-NMR spectra were recorded on Perkin Elmer R12 (60 MHz) and R32 (90 MHz) and Bruker WP80 (80 MHz) and WH360 (360 MHz) instruments and ^{13}C NMR spectra on Bruker WM80 (20.15 MHz) and WH360 (90.55) instruments. J Values are recorded in Hz. Combuston analyses were recorded by Mrs G. Olney and Miss K. Plowman, University of Sussex, and mass spectra on Kratos MS25 or MS80 spectrometers using electron impact (EI) ionisation by Mr A. Greenway, University of Sussex. Thin layer chromatography was carried out using Kieselgel GF_{254} (Merck) and preparative chromatography using silica PF_{254} for flash columns or silica PF_{254} (Merck) in 1.2 or 4 mm thickness on a chromatotron (Harrison Research). Deuterium gas was supplied by Argo International Ltd.

Hydrogenative Rearrangement of Diethyl 2-Isopropenyl-4-oxo-1-thia-3-azabicyclo[4.2.0]octa-5,7-diene-2,7-dicarboxylate (**2**, $R^1 = R^2 =$ Et) - A solution of the thiazetidine (**2**, $R^1 = R^2 =$ Et)[3] (50 mg, 0.16 mmol) in dry ethanol (20 cm^3) was hydrogenated at room temperature and pressure using Adams catalyst (10 mg). After 3 hours, hydrogen uptake (3.2 cm^3) had ceased and the solution was filtered through Celite. The solvent was removed *in vacuo* to yield a pale oil, which was purified by chromatography (chromatotron; silica; ether / petroleum ether ,3:1). The resulting white solid was recrystallised from chloroform / petroleum ether to yield white plates; (48 mg, 96%); mp 105-107 °C. The product had analytical and spectroscopic data identical to those of an authentic sample of the thiazolidine (**3**, $R^1 = R^2 =$ Et) prepared by cyclisation of the thiazolidine diester (**5**, $R^1 = R^2 =$ Et) with propiolic acid.[4]

Hydrogenative Rearrangement of Diethyl 2-Isopropenyl-4-oxo-1-thia-3-azabicyclo[4.2.0]oct-7-ene-2,7-dicarboxylate (**6**, $R^1 = R^2 =$ Et) - A solution of the thiazetidine (**6**, $R^1 = R^2 =$ Et)[3] (50 mg, 0.15 mmol) in dry ethanol (20 cm^3) was hydrogenated using Adams catalyst (15 mg) at room temperature and atmospheric pressure. After 4 hours, hydrogen uptake (*ca.* 4.5 cm^3) had ceased and the suspension was filtered through Celite. The solvent was removed *in vacuo* to yield an off-white solid which was purified by chromatography (chromatotron; silica; ether / petroleum ether, 1:4). The resulting solid was recrystallised from chloroform / petroleum ether to yield white needles of **diethyl 6,7-dihydro-2,2-dimethyl-5-oxo-5H-thiazolo[3.2-a]pyridine-3,8-dicarboxylate** (**7**, $R^1 = R^2 =$ Et) (30 mg, 60%); mp 121-122 °C; (Found: C, 55.0; H, 6.3; N, 4.05. $C_{15}H_{21}NO_5S$ requires C, 55.05; H, 6.4; N, 4.3%); m/z 327 (M^+); λ_{max} / nm 242, 303 and 311(sh) (log ε 4.63, 4.78, and 4.75); ν_{max} (KBr) / cm^{-1} 1740 (ester), 1690 (conjugated ester) and 1660 (amide); δ_H (C^2HCl_3, 60 MHz) 1.22 (6H, t, J 7.3, 2 x OCH_2CH_3), 1.47 (3H, s, *anti-*CH_3), 1.51 (3H, s, *syn-*CH_3), 2.6 (4H, brs, 2 x CH_2), 4.11 (4H, q, J 7.3, 2 x OCH_2) and 4.6 (1H, s, *CH*); δ_C (C^2HCl_3, 90.55 MHz) 14.19 and 14.48 (2 x $OCH_2C\,H_3$), 21.02 (*anti-C* H_3), 24.17 (*syn -C* H_3), 30.82 (-*C* H_2), 32.96 (-*C* H_2),

50.67 [$(CH_3)_2C$ S], 60.55 and 61.79 (2 x O*C* H_2), 69.45 (H), 99.08 (*C* =), 151.47 (*C* =), 166.79 (amide *C* =O) and 167.76 and 169.18 (2 x ester *C* =O).

Alternative Synthesis of Diethyl 2,3-Dihydro-2,2-dimethyl-5-oxo-5H-thiazolo[3,2-a]pyridine-3,8-dicarboxylate (**6**, $R^1 = R^2$ = Et) - To a solution of ethyl 2-ethoxycarbonylmethylene-5,5-dimethyl thiazolidine 4-carboxylate (**5**, $R^1 = R^2$ = Et)[4] (19 mg, 0.07 mmol) in dry dichloromethane (2 cm^3) was added successively, DCCD (20 mg, 0.09 mmol) and acrylic acid (15 mg, 0.2 mmol) in dry dichloromethane (1 cm^3) under nitrogen at room temperature with stirring. Stirring was continued for six hours at room temperature until all the thiazolidine (**4**, $R^1 = R^2$ = Et) had reacted (tlc; silica; ether / petroleum ether 3:1). The solvent was removed *in vacuo* and the residue was taken up in chloroform and passed through a short alumina column (Woelm, neutral, grade I). The resulting white solid was purified by chromatography (chromatotron; silica; ether / petroleum ether 1:4 as white prisms, (15 mg, 66%), mp 120-122 °C, undepressed on admixture with the sample prepared by hydrogenolytic rearrangement. The infrared spectra of the two samples (KBr) were identical

Hydrogenative Rearrangement of Diethyl 2-Isopropenyl-4-oxo-1-thia-3-azabicyclo[4.2.0]octa-5,7-diene-2,7-dicarboxylate (**2**, $R^1 = R^2$ = Et) **using Deuterium Gas** - The thiazetidine (**2**, $R^1 = R^2$ = Et)[3] (30 mg, 0.93 mmol) was dissolved in (O-$^2H_1$)-ethanol (3 cm^3) and reduced using deuterium gas and Adams catalyst (15 mg) at room temperature and atmospheric pressure. After 3 hours, uptake of deuterium had ceased and the solution was filtered through Celite. The solvent was removed *in vacuo* to yield a crude solid which was purified by chromatography (chromatotron; silica; ether / petroleum ether, 1:3). Removal of the solvent *in vacuo* yielded a white solid which was recrystallised from chloroform / petroleum ether to yield the thiazolidines **8** and **9** as white prisms; (19 mg, 63%); mp 105-107 °C; m/z 327 (M^+); δ_H (C^2HCl_3, 360 MHz) 1.30 and 1.37 (2 x 3H, 2 x t, J 7.1, 2 x OCH_2CH_3), 1.57 (s, *anti*-CH_2 ^2H), 1.59 (s, *anti*-$CH3$), 1.66 (s, *syn*-CH_2 ^2H), 1.68 (s, *syn*-CH_3), 4.27 and 4.33 (2H, q, J 7.1, 2 x CH_2 O), 6.25 (1H, d, J 9.5, pyridone α-*CH*) and 7.88 (1H, d, J 9.5, pyridone β-*CH*); δ_C (C^2HCl_3,90.5 MHz) 14.14 and 14.39 (2 x OCH_2C H_3), 23.54, (t, *anti*-C $H_2{}^2H$), 23.77 (*anti*-C H_3), 32.80 (t, *syn*-C $H_2{}^2H$), 33.06 (*syn*-C H_3), 51.13 (s, $(CH_3)_2C$) 61.24 and 62.17 (2 x CH_2O), 114.07 (pyridone α-*C*), 140.21 (pyridone β-*C*), 157.38 (*C* =), 162.07 (pyridone *C* =O) and 164.58 and 166.51 (ester *C* =O).

Palladium Catalysed Rearrangement of Diethyl 2-Isopropenyl-4-oxo-1-thia-3-azabicyclo-[4.2.0]octa-5,7-diene-2,7-dicarboxylate (**2**, $R^1 = R^2$ = Et) **Using Deuterium Gas** - A solution of the thiazetidine (**2**, $R^1 = R^2$ = Et)[3] (10 mg, 0.03 mmol) in ethyl acetate (2 cm^3) was reduced using deuterium gas with 10% palladium on charcoal catalyst (10 mg) at room temperature and atmospheric pressure. The solution was stirred overnight and filtered through Celite. The solvent was removed *in vacuo* to yield a crude solid which was purified by chromatography (chromatotron; silica; ether / petroleum ether, 3:1). The purified material crystallised on tituration with ether (6 mg, 60%), mp 106-107 °C. The ^{1}H-NMR spectrum was similar to that in the previous experiment, but the ratio of *syn:anti* deuteriation was 1:1.

Rearrangement of Diethyl 2-Isopropenyl-4-oxo-1-thia-3-azabicyclo[4.2.0]octa-5,7-diene-2,7-dicarboxylate (**2**, $R^1 = R^2$ = Et) **Using Tris(triphenylphosphine)rhodium(I)** - The thiazetidine (**2**, $R^1 = R^2$ = Et)[3] (15 mg, 0.046 mmol) was stirred in a solution of dry benzene (2 cm^3) with tris(triphenylphosphine)

rhodium(I) chloride (10 mg) under a hydrogen atmosphere overnight. The solvent was removed *in vacuo* to yield a red oil which was purified by chromatography (chromatotron; silica; ether/petroleum ether 3:1) to yield the thiazine (**1**, $R^1 = R^2 = Et$) as a white solid which was recrystallised from chloroform/ether (11 mg, 73%); mp 150-152 °C, undepressed on admixture with an authentic sample of the thiazine (**1**, $R^1 = R^2 = Et$).[4] ^{1}H-NMR (90 MHz) and IR (KBr) spectra were identical to those of an authentic sample of the thiazine (**1**, $R^1 = R^2 = Et$).[4]

Reaction of Ethyl 2-Ethoxycarbonylmethyl-1-formyl-4-isopropenyl-1,3-thiazetidne-2,4-carboxylate (10) with Tris(triphenylphosphine)rhodium(I) - The reduced thiazetidine **10**[3] (60 mg, 0.19mmol)) was dissolved in dry ethyl acetate (2 cm^3) with tris(triphenylphosphine)rhodium(I) chloride (23 mg). The solution was stirred overnight at room temperature and filtered through Celite. The solvent was removed *in vacuo* and the residue was chromatographed (chromatotron : diethyl ether) to give a clear homogeneous oil (24 mg, 40%), which had identical spectra to those of an authentic sample of ethyl 2-ethoxycarbonylmethyl-3-formyl-2,3-dihydro-5-methyl-6H-1,3-thiazine-4-carboxylate (**11**).[3]

Condensation of Ethyl 5-Ethoxycarbonyl-1-methyl-2-thia-4-azabicyclo[3.1.0]hex-3-en-3-yl acetate (12) with Propiolic Acid - Ethyl 5-ethoxycarbonyl-1-methyl-2-thia-azabicyclo[3.1.0]hex-3-en-3-yl-acetate **12** (0.74 g, 2.73 mmol), propiolic acid (0.23 g, 3.3 mmol) and DCCD (0.68 g, 3.3 mmol) in dry dichloromethane (20 cm^3) were stirred under nitrogen at room temperature overnight. The suspension was filtered to remove dicyclohexyl urea and the solvent was removed *in vacuo*. The crude material was purified by chromatography (chromatotron; silica; ether / petroleum ether, 3:1) to yield the tricyclic compound **13** as a solid (0.83 g, 94%) mp 92-94 °C; (Found: C, 55.7; H, 5.5; N, 4.2. $C_{15}H_{17}NO_5S$ requires: C, 55.7; H, 5.3; N, 4.3%); m/z 323 (M^+); λ_{max} / nm 281(sh), 289, 325 and 341 (log ε 3.89, 3.97, 3.72 and 3.59); ν_{max} (KBr) / cm^{-1} 1735 (ester) 1690 (conjugated ester) and 1655 (pyridone); δ_H (C^2HCl_3, 90 MHz) 1.24 and 1.33 (3H, t, J 7, 2 x OCH_2CH_3), 1.26 (1H, d, J 6.6, cyclopropyl *CH*), 1.56 (3H, br s, CH_3), 2.22 (1H, d, J 6.6, cyclopropyl *CH*), 4.27 and 4.29 (2H, q, J 7, 2 x OCH_2 CH_3), 6.20 (1H, d, J 9.4, pyridone α-*CH*) and 7.78 (1H, d, J 9.4, pyridone β-*CH*); δ_C (C^2HCl_3, 20.15 MHz, not all absorptions visible) 14.23 (q, 2 x OCH_2C H_3), 17.66 (q, *C* H_3), 22.85 (t, cyclopropyl *C* H_2), 61.31, 62.34 (t, 2 x *OC* H2), 113.94 (d, pyridone α-*C*) and 139.34 (pyridone β-*C*).

Ethyl 2,5-Dioxo-3-isopropyl-2H,3H,5H-thiazolo[3,2a]-pyridine-8-carboxylate (17, R^1 = Et) - On one occasion only, during the hydrogenative rearrangement of diethyl 2-(1-methylethanyl)-4-oxo-1-thia-3-azabicyclo[4.2.0]octa-5,7-diene-2,7-dicarboxylate (**2**, $R^1 = R^2 = Et$), a second product was obtained which was identified as ethyl 3-isopropyl-2,5-dioxo-2H,3H,5H-thiazolidino[3,2-a]pyridine-8-carboxylate (**17**, $R^1 = Et$); 48%; mp 134 °C; (Found: C, 55.2; H, 5.5; N, 4.5. $C_{13}H_{15}NO_4S$ requires: C, 55.5; H, 5.4; N, 5.0%); m/z 281 (M^+); λ_{max} (pH 7) / nm 273, 280, 315, 322 and 333 (log ε 4.10, 4.08, 3.78, 3.84, and 3.72); λ_{max} (pH14) / nm 315 and 352 (log ε 4.27 and 4.32) ; δ_H (C^2HCl_3, 80 MHz) 0.84 (3H, d, J 7, CH_3) 1.20 (3H, d, J 7, CH_3) , 1.34 (3H, t, J 7.2, OCH_2) 2.96 (1H, m, *CH* $(CH_3)_2$), 4.32 (2H, q, J 7.2, OCH_2), 4.84 (1H, d, J 3.6, *CH*), 6.38 (1H, d, J 9.7, pyridone α-*CH*) and 7.91 (1H, d, J 9.7, pyridone β-*CH*); δ_C (C^2HCl_3, 90.55 MHz) 14.31 (*C* H_3), 15.48 (*C* H_3), 17.55 (*OC* H_2CH_3), 29.60 (*C* $H(CH_3)_2$), 61.77 (*OC* H_2), 71.32 (*C* H), 105.73 (N-*C* =), 116.39 (pyridone α-*C*) 138.98 (pyridone β-*C*) 152.83 (N-*C* -S) 160.42 (pyridone *C* =O) 163.92 (ester *C* =O) and 196.57 (S-*C* =O).

Hydrogenative Rearrangement of Methyl 8-Benzyloxycarbonyl-3-isopropenyl-5-oxo-2-thia-4-azabicyclo[4.2.0]octa-6,8-diene-3-carboxylate (**2**, R^1 = Ph CH_2, R^2 = Me). **Method A, Adams Catalyst.** - A solution of the thiazetidine (**2**, $R^1 = PhCH_2$, R^2 = Me) (100 mg, 0.27 mmol) in ethanol (25 cm^3) was hydrogenated at room temperature and pressure using Adams catalyst (20 mg) for 6 hours. The solution was filtered through Celite and the solvent was removed *in vacuo* to yield a brown oil which was chromatographed (silica gel, ether/petroleum ether, 1:2) to yield two components. The first component from the column, **methyl 8-benzyloxycarbonyl-2,2-dimethyl-5-oxo-2H,3H,5H-thiazolo[3,2-a]pyridine-3-carboxylate** (**3**, $R^1 = PhCH_2$, R^2 = Me) was isolated as a yellow gum (25 mg, 25%); m/z 373 (M^+); λ_{max} / nm 241 and 300 (log ε 3.89 and 4.07); ν_{max} (film) / (cm^{-1}) 1737 (ester) 1708 (ester) and 1676 (amide); δ_H(C^2HCl_3, 360 MHz) 1.57 (3H, s, *CH3*), 1.68 (3H, s,*CH3*), 3.80 (3H, s, O*CH3*), 5.14 (1H, s, *CH*-OCH_3), 5.31 (2H, s, *CH2* Ph), 6.24 (1H, d, J 9.5, pyridone α-*CH*), 7.39 (5H, m, phenyl) and 7.90 (1H, d, J 9.5, pyridone β-CH). The second component from the column, **benzyl 2,5-dioxo-3-isopropyl-2H,3H,5H-thiazolo-[3,2-a] pyridine-8-carboxylate** (**17**, $R^1 = PhCH_2$) was an off-white solid (54 mg, 58%); mp 105-106 °C; (Found: C, 59.35; H, 5.65%; N, 4.3. $C_{18}H_{17}NO_4S$. H_2O requires: C, 59.8; H, 5.3; N, 3.9%); m/z 343 (M^+); λ_{max} (pH 7) / nm 273, 280 and 321 (log ε 4.20, 4.20 and 3.98); λ_{max} (pH 14) / nm 318 and 350 (log ε 4.12 and 4.20); ν_{max} (KBr) / cm^{-1} 1702 (ester) and 1664 (amide); δ_H(C^2HCl_3, 360 MHz) 0.86 (3H, d, J 7, *CH3*), 1.22 (3H, d, J 7, *CH3*), 2.98 (1H, m, *CH* $(CH_3)_2$), 4.87 (1H, d, J 3.6, N-*CH*), 5.32 (2H, AB, *CH2* Ph), 6.39 (1H, d, J 9.7, pyridone α-*CH*) 7.39 (5H, m, phenyl) and 7.95 (1H, d, J 9.7, pyridone β-*CH*); δ_C (C^2HCl_3, 90.55 MHz) 15.47 (*C* H_3), 17.54 (*C* H_3), 29.60 (*C* H$(CH_3)_2$), 67.46 (*C* H_2Ph) 71.34 (N-*C* =C), 116.42 (pyridone α-*C*), 128 (phenyl), 135.34 (N-*C* -S), 138.97 (pyridone β-*C*) and 160.36, 163.77 and 196.40 (3 x *C* =O).

Method B, 5% Rhodium on Alumina. - A solution of the thiazetidine, (**2**, $R^1 = PhCH_2$, R^2 = Me), (100 mg, 0.27 mmol) in ethanol (25 cm^3) was hydrogenated at room temperature and pressure using 5% rhodium on alumina (20 mg) for 6 hours. The solution was filtered through Celite and the solvent was removed *in vacuo* to yield a brown oil which was chromatographed (silica gel, ether/petroleum ether) to yield three components. The first component, **benzyl 2,5-dioxo-3-isopropylidene-2H,3H,5H-thiazolo-[3,2-a]pyridine-8-carboxylate** (**18**, $R^1 = PhCH_2$), eluted first from the column in petroleum ether / ether (2:1) as a yellow gum (32 mg, 35%); m/z 341 (M^+); ν_{max}(film) / cm^{-1} 1700 (ester), 1654 (amide) and 1592 (thioamide); δ_H (C^2HCl_3, 80 MHz (ppm) 1.95 (3H, s, *CH3*), 2.40 (3H, s, *CH3*), 5.33 (2H, s, *CH2* Ph), 6.38 (1H, d, J 9.7, pyridone α-*CH*), 7.39 (5H, m, phenyl) and 7.90 (1H, d, J 9.7, pyridone β-*CH*). The second component from the column, **benzyl 2,5-dioxo-3-isopropenyl-2H,3H,5H-thiazolo[3.2-a]-pyridine-8-carboxylate** (**19**, $R^1 = PhCH_2$), eluted from the column in petroleum ether: diethyl ether (3:2) as a yellow oil (9 mg, 10%); m/z 341 (M^+); λ_{max} / nm 234, 274, 281(sh), 310 and 320(sh) (log ε 3.51, 3.90, 3.88, 3.61 and 3.61), ν_{max} (film) / cm^{-1} 1700 (ester), 1668 (amide) and 1595 (thioamide); δ_H (C^2HCl_3) 360 MHz) 1.86 (3H, s, *CH3*), 4.92 (1H, s, N-*C* H), 5.13, 5.26 (2H, 2 x s, vinyl *CH2*), 5.31 (2H, 2 x s, *CH2* Ph), 6.38 (1H, d, J 9.7, pyridone α-*CH*), 7.39 (5H, m, phenyl) and 7.95 (1H, d, J 9.7, pyridone β-*CH*). Other absorptions were present. The final product, methyl 2,2-dimethyl-5-oxo-2H,3H,5H-8-benzyloxycarbonyl-thiazolo[3.2-a]pyridine-3-carboxylate (**3**, $R^1 = PhCH_2$, R^2 = Me), eluted from the column in petroleum ether / diethyl ether 1:1 and was isolated as a yellow gum (19 mg, 19%). The spectra indicated identity with the product obtained in method A above.

Ethyl 8-Benzyloxycarbonyl-3-isopropenyl-5-oxo-2-thia-4-azabicyclo-[4.2.0]- octa-6,8-diene-3-carboxylate (2, R^1 = $PhCH_2$, R^2 = Et) - The benzyl ethyl pyridone (1, R^1 = $PhCH_2$, R^2 = Et) (100 mg, 0.26 mmol) in dry degassed benzene (350 cm^3) was irradiated at 8 °C with a 125W high pressure immersion mercury arc lamp through Pyrex filters under nitrogen overnight. The benzene was removed *in vacuo* to yield a pale oil which was chromatographed (silica gel, ether/petroleum ether 1:2) to give the thiazetidine (2, R^1 = $PhCH_2$, R^2 = Et), as foam (62 mg, 62%); m/z 385 (M^+); λ_{max} / nm 292 and 310 (log ε 3.91 and 3.75); ν_{max} (film) / cm^{-1} 1745 (ester), 1720 (conjugated ester) and 1675 (amide); δ_H (C^2HCl_3, 360 MHz) 1.25 (3H, t, J 7, CH_2CH_3), 1.99 (3H, s, CH_3), 4.26 (2H, q, J 7, CH_2 CH_3), 5.21 (2H, s, CH_2 Ph), 5.36, 5.62 (2H, 2 x s, C=CH_2), 6.21 (1H, d, J 10, pyridone α-*CH*), 7.31 (5H, m, phenyl) and 7.71 (1H, d, J 10, pyridone β-*CH*). δ_C(C^2HCl_3, 90.55 MHz) 13.60 (CH_2C H_3), 19.04 (*C* H_3), 63.22 (O*C* H_2), 66.52 (*C* H_2Ph), 103.75 (N-*C*-S), 116.10 (pyridone α-*C*), 120.41 (C=*C* H2), 128.24 (phenyl), 135.87 (C=CH2), 138.97 (pyridone β-C), 156.59 (N-C=C) and 158.34, 162.92 and 164.45 (3 x *C* =O).

Hydrogenation of Ethyl 8-Benzyloxycarbonyl-3-isopropenyl-5-oxo-2-thia-4-azabicyclo-[4.2.0]octa-6,8-diene-3-carboxylate (2, R^1 = $PhCH_2$, R^2 = Et) - A solution of the thiazetidine (2, R^1 = $PhCH_2$, R^2 = Et) (100 mg, 0.26 mmol) in ethanol (25 cm^3) was hydrogenated at room temperature and pressure using Adams catalyst (20 mg) for 6 hours. The solution was filtered through Celite and the solvent was removed *in vacuo* to yield a brown oil which was chromatographed (silica gel, ether/petroleum ether 1:2) to yield two components. The first was identified as **the thiolactone** (17, R^1 = $PhCH_2$) (38 mg, 41%) with spectra consistent with those of the authentic sample prepared as described above. The second component was isolated as a yellow oil (35 mg, 35%) and was evidently **benzyl ethyl 2,2-dimethyl-5-oxo-2H,3H,-5H-thiazol[3,2-a]pyridine-3,8-dicarboxylate** (3, R^1 = $PhCH_2$, R^2 = Et); m/z 387.1115 ($C_{20}H_{21}NO_5S$ requires: 387.1140); λ_{max} / nm 286 and 321 (log ε 3.82 and 3.60); ν_{max} (film) / cm^{-1} 1747 (ester), 1702 (ester) and 1662 (amide); δ_H (C^2HCl_3, 360 MHz (ppm) 1.27 (3H, t, J 7.2, CH_2CH_3), 1.56 (3H, s, CH_3), 1.65 (3H, s, CH_3), 4.24 (2H, q, J 7.2, CH_2 CH_3), 5.10 (1H, s, N-*CH*), 5.28 (2H, s, CH_2 Ph), 6.21 (1H, d, J 9.6, pyridone α-*CH*), 7.38 (5H, m, phenyl) and 7.87 (1H, d, J 9.6, pyridone β-*CH*). A third component (30 mg) was shown to be unreacted starting material from its spectroscopic data.

2-Isopropenyl-4-oxo-1-thia-3-azabicyclo[4.2.0]octa-5,7-diene-2,7-dicarboxylic acid (2, R^1 = R^2 = H) - The diethyl pyridothiazetidine (2, R^1 = R^2 = Et) (250 mg, 0.77 mmol) was dissolved in ethanol (25 cm^3) and to this was added aqueous potassium hydroxide (7.7 cm^3, 0.1 molar). The solution was stirred for two days at room temperature and was partitioned between aqueous sodium bicarbonate and ether. The bicarbonate layer was acidified to pH 1 with conc. HCl and extracted with ethyl acetate. The ethyl acetate fraction was dried (Na_2SO_4), and the solvent was removed *in vacuo* to give a brown gum. This was recrystallised from ether to give an off-white foam which collapsed on standing (145 mg, 70%); m/z 267 (M^+); λ_{max} (pH 7) / nm 275, 314 and 326 (log ε 4.15, 3.79 and 3.65); λ_{max} (pH 14) / nm 266, 320 and 330 (log ε 4.15, 3.92 and 3.78); δ_H (C^2HCl_3, 360 MHz) 1.91 (3H, s, CH_3), 5.29 (1H, s, olefinic *CH*), 5.57 (1H, s, olefinic *CH*), 6.14 (1H, d, J 9.8, pyridone α-*CH*) and 7.63 (1H, d, J 9.8, pyridone β-*CH*); δ_C [C^2HCl_3/$(C^2H_3)_2SO$, 90.55 MHz] 18.62 (CH_3), 105.11 (N-*C* =), 115.22 (=*C* H_2), 119.04 (pyridone α-*C*), 135.74 (*C* =), 139.96 (pyridone β-*C*), 156.52 (N-*C* -S) and 159.32, 164.84 and 165.91 (3 x *C* =O).

2,5-Dioxo-3-isopropyl-2H,3H,5H-thiazolo[3,2-a]pyridine-8-carboxylic acid (17, R = H) - A solution of the thiazetidine (2, $R^1 = R^2 = H$) (100 mg, 0.37 mmol) in ethanol (25 cm^3) was hydrogenated overnight at room temperature and pressure using Adams catalyst (25 mg). The solution was filtered through Celite and the solvent was removed *in vacuo* to yield a brown oil which 'crystallised' from ether to give an off-white foam which collapsed to a gum on standing (23 mg, 25%); λ_{max} / nm 268 and 322; δ_H (C^2HCl_3, 360 MHz) 0.54 (3H, d, J 7, *CH3*), 0.86 (3H, d, J 7, *CH3*), 2.60 (1H, m, $CH_3CH\ CH_3$), 4.54 (1H, d, J 4, N-*CH*), 6.06 (1H, d, J 9, pyridone α-*CH*) and 7.60 (1H, d, J 9, pyridone β-*CH*).

2,2-Dimethyl-5-oxo-2H,3H,5H-thiazolo[3,2-a]pyridine-3,8-dicarboxylic acid (3, $R^1 = R^2 = H$) - To a solution of the thiazetidine (2, $R^1 = R^2 = H$) (100 mg, 0.37 mmol) in ethanol (25 cm^3) was added potassium hydroxide (3.7 cm^3 of a 0.1 molar solution in ethanol). The solution was hydrogenated overnight at room temperature and pressure using Adams catalyst (25 mg). The solution was filtered through Celite and the solvent was removed *in vacuo*. The residue was dissolved in aqueous sodium bicarbonate, which was acidified to pH 1 (conc. HCl) and then extracted into ethyl acetate. The ethyl acetate layer was then dried (Na_2SO_4) and the solvent was removed *in vacuo* to yield a brown oil, which crystallised from ether to give a pale brown solid, which could not be completely purified (19 mg, 19%); λ_{max} (pH 7) / nm 283 and 322 (log ε 4.06 and 3.93); λ_{max} (pH 14) / nm 271 and 327; δ_H (C^2HCl_3-$(C^2H_3)_2SO$; 360 MHz; all peaks were broad), 1.52 (3H, s, *CH3*), 1.55 (3H, s, *CH3*), 4.95 (1H, s, N-*CH*), 6.08 (1H, d, J 7, pyridone α-*CH*) and 7.34 (1H, d, J 7, pyridone β-*CH*).

Ethyl 2-Hydroxy-3-isopropenyl-5-oxo-2H,3H,5H-thiazolo[3,2-a]pyridine-8-carboxylate (20) - Diethyl 3-isopropenyl-5-oxo-2-thia-4-azabicyclo[4.2.0]octa-6,8- diene-3,8-dicarboxylate (2, $R^1 = R^2 = Et$) (100 mg, 0.31 mmol) was dissolved in THF (10 cm^3) and sodium borohydride (25 mg) was added. Water (1 cm^3) was slowly added and the solution was left stirring at room temperature. After 3 hours, a further portion of water (5 cm^3) was added and the excess borohydride was destroyed with conc. HCl. The solution was extracted with chloroform and the organic layer was washed with water, dried (Na_2SO_4) and the solvent was removed *in vacuo* to give a clear oil. This was chromatographed (chromatotron, ether) to give an off-white foam which collapsed to a gum on standing (61 mg, 70%); m/z 281.0731 ($C_{13}H_{15}NO_4S$ requires: 281.0722); λ_{max} / nm 281 and 318 (log ε 3.92 and 3.66); ν_{max} (film) / cm^{-1} 3600-3100 (OH), 1710 (ester) and 1650 (amide); δ_H(C^2HCl_3, 360 MHz) 1.33 (3H, t, J 7, CH_2CH_3), 1.83 (3H, s, *CH3*), 4.29 (2H, 2 x q, J 7, *CH2* CH_3), 4.43 (1H, s, vinyl *CH*), 4.86 (1H, s, vinyl *CH*), 5.21 (1H, br, slowly exchangeable, *OH*), 5.36 (1H, s, N-*CH*), 5.43 (1H, s, S-*CH*), 6.12 (1H, d, J 9, pyridone α-*CH*) and 7.77 (1H, d, J 9, pyridone β-*CH*).

Ethyl [2,3-$^2H_2$]-2-Hydroxy-3-isopropenyl-5-oxo-2H,3H,5H-thiazolo-[3,2-a]pyridine-8-carboxylate (21) - Diethyl 3-isopropenyl-5-oxo-2-thia-4-azabicyclo[4.2.0]octa-6,8-diene-3,8-dicarboxylate (2, $R^1 = R^2 = Et$) (100 mg, 0.31 mmol) was dissolved in THF (10 cm^3) and to this was added sodium borodeuteride (22mg). ^2H_2O (1 cm^3) was then slowly added and the solution was left stirring at room temperature. After 3 hours a further portion of ^2H_2O (5 cm^3) was added and the excess borodeuteride was destroyed with dil. ^2HCl. The solution was extracted with chloroform, the organic layer was washed with water and dried (Na_2SO_4). The solvent was removed *in vacuo* to give a clear oil. This was chromatographed (chromatotron, ether) to give an off-white foam (56 mg, 64%); m/z 283 (M^+); ν_{max} (film) / cm^{-1} 1703 (ester) and 1645 (amide); δ_H (C^2HCl_3, 80 MHz) 1.33 (3H, t, J 7.1, OCH_2CH_3), 1.82 (3H, s, *CH3*), 4.26 (2H, dq, J

7.1, O*CH*$_2$ CH$_3$), 4.42 (1H, s, olefinic *CH*), 4.85 (1H, s, olefinic *CH*), 6.10 (1H, d, J 9.4, pyridone α-*CH*), and 7.76 (1H, d, J 9.4, pyridone β-*CH*); δ_C (C^2HCl_3, 90.55 MHz (ppm) 14.35 (OCH$_2$*C* H$_3$), 19.91 (*C* H$_3$), 61.42 (O*C* H$_2$), 75.12 (t, N-*C* -D), 80.68 (t, S-*C* D), 104.88 (*C* =), 112.84 (*C* =), 113.93 (pyridone α-*C*), 137.06 (N-*C* =), 140.38 (pyridone β-*C*), 156.62 (N-*C* -S), 161.92 (pyridone *C* =O) and 164.52 (ester *C* =O).

Ethyl 2-Hydroxy-3-isopropyl-5-oxo-2H,3H,5H-thiazolo[3,2-a]pyridine-8-carboxylate (22). Method A - From the Thiolactone (**17**, R^1 = Et) - The thiolactone (**17**, R^1 = Et) (80 mg, 0.28 mmol) was dissolved in THF (10 cm^3) and sodium borohydride (15 mg) was added. Water (1 cm^3) was slowly added and the solution was left stirring at room temperature. After 3 hours a further portion of water (5 cm^3) was added and the excess borohydride was destroyed with conc. HCl. The solution was extracted with chloroform, the organic layer was washed with water, and dried (Na_2SO_4). The solvent was removed *in vacuo* to give a pale oil. This was chromatographed (chromatotron, ether) to give an off-white solid, which was recrystallised from ethanol (55 mg, 68%); m.p. 133-134 °C; m/z 283.0868 ($C_{13}H_{17}NO_4S$ requires 283.0878); λ_{max} / nm 230, 285 and 318 (log ε 3.68, 3.98 and 3.75); ν_{max} (KBr) / cm^3 3600-3100 (OH), 1712 (ester) and 1650 (amide); δ_C (C^2HCl_3, 360 MHz) 0.81 (3H, d, J 7, *CH*$_3$), 1.04 (3H, d, J 7, *CH*$_3$), 1.34 (3H, t, J 7.1, OCH$_2$*CH*$_3$), 2.36 (1H, m, *CH* (CH$_3$)$_2$), 4.28 (2H, q, J 7, O*CH*$_2$), 4.97, 1H, d, J 5, N*CH*), 5.47 (1H,s, S*CH*), 5.59 (1H, br, *OH*), 6.07 (1H, d, J 9.4, pyridone α-*CH*) and 7.71 (1H, d, J 9.4, pyridone β-*CH*); δ_C (C^2HCl_3, 90.55 MHz) 14.40 (*C* H$_3$), 17.09 (*C* H$_3$), 19.05 (OCH$_2$), 28.32 (*C* H(CH$_3$)$_2$), 61.30 (O*C* H$_2$), 76.51 (N-*C* H), 77.97 (S-*C* H), 113.82 (pyridone α-*C*) and 140.01 (pyridone β-*C*).

Method B - From the Thiolactol (20) - The thiolactol (**20**) (65 mg, 0.23 mmol) was dissolved in ethanol (15 cm^3) and hydrogenated at room temperature and pressure using Adams catalyst (20 mg) for 6 hours. The solution was filtered through Celite and the solvent was removed *in vacuo* to yield a pale brown oil which was chromatographed (chromatotron, ether / petroleum ether 2:1) to yield an off-white solid (37 mg, 57%) with spectra which were identical to those of the compound obtained using method A.

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