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STEREOSELECTIVE SYNTHESIS OF HETEROCYCLES BY DESULFURISATION OF CONDENSED THIAZOLIDIN-2-ONES[1]

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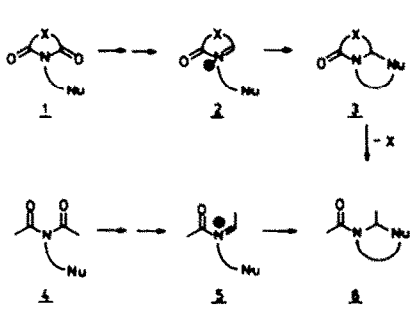
Abstract - Elimination of the S atom in fused thiazolidines e.g. **7** or **9** has been investigated using three methods. Whereas LAH reduction gave the corresponding thiazolidines and H_2O_2/HCOOH oxidation the S,S-dioxides both types of compound could not be further degraded. Ra-Ni treatment of thiazolidinones provided in all cases good yields of desulfurised products. In this manner stereoselective syntheses of piperidine **17** and pyrrolidine **19** become easily possible.

The development of the N-acyliminium cyclisation technique in our laboratories has led to a simple and versatile route to a variety of heterocyclic systems.[2] All cyclisation reactions leading to the latter heterocycles start from a π-nucleophile connected to an imide ring as in **1**, whereupon the nucleophile is cyclised onto the starting ring via the N-acyliminium intermediate **2** to give the product **3**. Consequently, all products derived in this manner are at least bicyclic. Therefore, the question remains whether monocyclic products are also accessible via the iminium technique. An obvious approach would be to start from a linear precursor **4**; from this the monocyclic **6** would then be available via **5**. However, given the ready availability and easy manipulation of cyclic iminium precursors, preference is given to a cyclic imide as a starting unit[2b] which then should possess functionalities suitable for degradation of the initial ring in the product, i.e. a structural characteristic which allows the transformation **3** → **6**, leaving only the newly formed ring. It was anticipated that incorporation of an S atom in the initial imide ring[2c,d] would offer a "chemical handle" to allow a transformation in the desired direction. To this end, several types of transformations were carried out; either the S atom was removed directly, or it was chemically converted to a functional group supposedly better suited for removal and ring opening.

Reduction of the thiocarbamate carbonyl group

Removal of the S atom from the bicyclic ring system (i.e. the transformation **3** → **6**), where the S atom directly adjoins the amide moiety, can be carried out either with or without prior reduction of the thiocarbamate carbonyl group. In the first procedure this reduction proved to be possible upon treatment with $LiAlH_4$[3] (THF, reflux 17 hr). In the preliminary experiments an unexpected result was obtained for **7a** which afforded[4] the disulfide **8**. Formation of the disulfide was completely suppressed when, after mixing the substrate with the lithium aluminium hydride solution under a nitrogen atmosphere, dry oxygen was allowed to diffuse into the reaction vessel. In this manner, the cyclisation products **9a**, **10a**, **11a**, **12a** and **13a** could be reduced to **9b**, **10b**, **11b**, **12b** and **13b** respectively in yields up to 83%. The reduction products are readily identified from their spectral data: absence of a carbonyl absorption in the IR and the appearance of an AB quartet for the SCH_2N protons, J being 6 to 9 Hz. A further characteristic is found in the mass spectrum of these compounds where the M-76



Scheme 1.

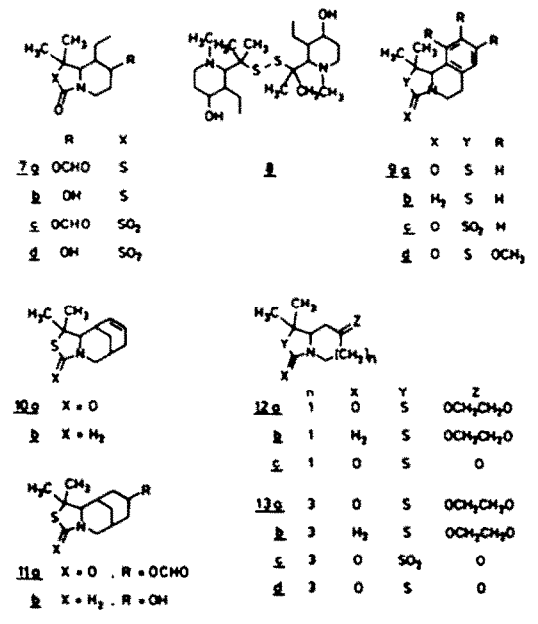


Fig. 1.

peak (loss of thioacetone) is prominent. Other, less reactive, metal hydrides could not effect the same transformation: e.g. reaction of **7a** with diisobutylaluminium hydride only reduced the ester function, affording **7b** in 71% yield, while **12a** with Red-al[R] (sodium bis(2-methoxy-ethoxy)aluminium hydride) gave no reaction.

To effect the desired ring opening, the products **9b**, **10b**, **11b**, **12b** and **13b** were treated with Raney nickel. However, the results were not unambiguous. Desulfurisation of **9b** afforded the tetrahydroisoquinoline **14a** in 63% yield, as could be concluded from the ^{1}H-NMR spectrum: the presence of an isopropyl group was demonstrated by a septet (J = 6.8 Hz) at 1.95 ppm and two doublets (J = 6.8 Hz) at 0.85 and 1.0 ppm respectively; clearly, the asymmetry at the benzylic position renders the two methyl groups diastereotopic. Furthermore, the N-methyl group at 2.45 ppm is an obvious feature by itself. In general, however, results in this series were non-reproducible, which probably can be ascribed to the presence of an amino function in the molecule.[5] Since the aforementioned compounds are in fact N,S acetals, ring opening might be effected by hydrolysis. Several methods using mercuric chloride as a catalyst[6] were attempted; however, only starting materials were recovered thereby reflecting the relative stability of acetals of formaldehyde.[7]

Oxidation of the S atom. S-Phenylthiocarbamates can be oxidised to arylsulfonic acids with hydrogen peroxide.[8] A comparable reaction has been described for aliphatic thiol esters.[9] The structural analogy of these compounds to the cyclisation products is obvious, and consequently this reaction was used for attempted ring opening. When thiocarbamates **7a** and **9a** were subjected to oxidation (H_2O_2/HCOOH, room temperature 17 hr), the sulfones **7c** and **9c** were obtained in about 85% yield. Their structures were apparent from the two sulfone absorptions in the IR, at 1310–1300 cm^{-1} and at 1150–1120 cm^{-1} respectively. The conversion **7a** → **7c** could also be effected with *m*-chloroperbenzoic acid ($CHCl_3$, room temperature 18 hr) as the oxidising agent[10] in 86% yield. H_2O_2/HCOOH oxidation of **7b** effected, apart from oxidation, formylation of the hydroxy group so that **7c** was also obtained in 61% yield. Conversion of **7b** to the hydroxy sulfone **7d** was achieved in 47% yield upon treatment with *m*CPBA. Upon H_2O_2/HCOOH oxidation of **13a** concomitant hydrolysis of the ketal function was observed so that the keto-sulfone **13c** was obtained in 70% yield. In all cases examined, only products with the ring structure intact were recovered. Attempts to effect ring degradation by hydrogenolysis of the sulfones with Raney nickel or by treatment with NaOMe/HOMe gave no positive results.

Desulfurisations. Reductive desulfurisation of a

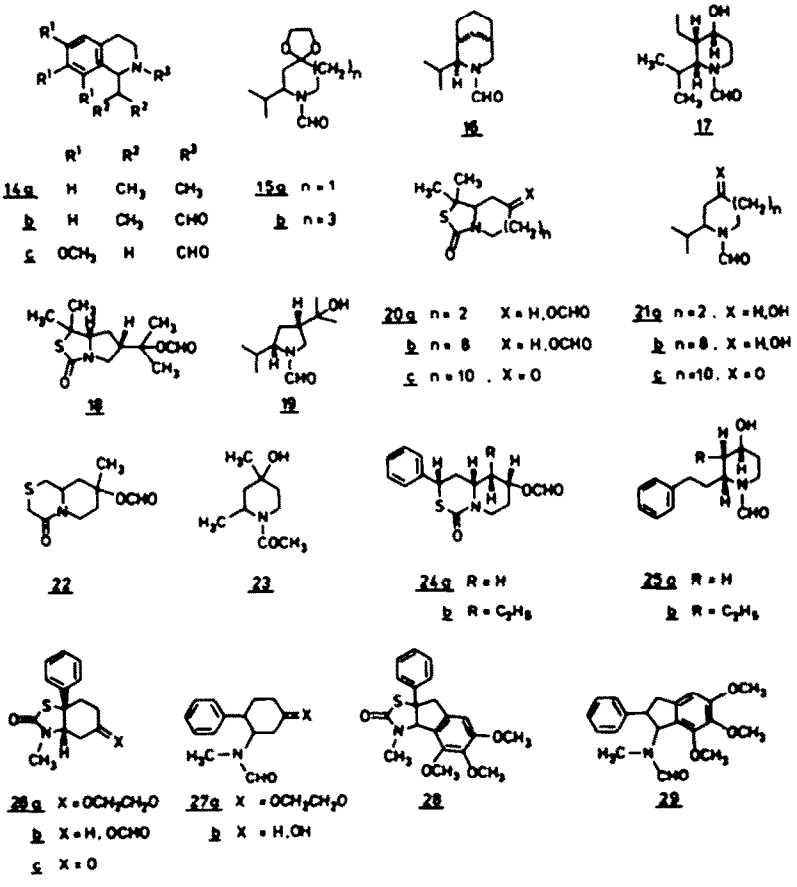


Fig. 2.

variety of sulfur compounds is a tool widely used in organic synthesis, as well as in industrial processes.[11] Many reagents have been used for this purpose, among them triethyl phosphite,[12] sodium in liquid ammonia[13] or lithium in ethylamide,[14] hydridocarbonylferrate ion,[15] tributyltinhydride,[16] sodium triethylborohydride/ferrous chloride,[17] and nickel boride.[18] However, the most effective and general hydrogenation catalyst still seems to be Raney nickel. This reagent, or an activated modification of it,[19] has been used on many types of S compounds,[20] e.g. mercaptanes, disulfides, sulfones, sulfoxides and thioketals, as well as cyclic sulfur compounds, notably thiophenes.[21] Desulfurisations of thiazolidine-2,4-diones[22] or 2-imino-thiazolidin-4-ones[23] have been carried out, mainly for the purpose of structure elucidation, giving amides as products. Under the reaction circumstances, the N-formyl C atom in the open chain imide intermediate is mostly lost in the product, although in some cases it can be retained.[24]

In analogy with these results, direct desulfurisation of the "thiocarbamate" cyclised compounds was attempted. Thus, refluxing the ketal **12a** with 10- to 20-fold excess by weight of Raney nickel in aqueous ethanol for 6 hr gave **15a** as an oil in 71% yield. Likewise, treatment of **13a** afforded the N-formylazocine **15b** in 81% yield.

Similarly, the tetrahydroisoquinolines **14b** and **14c** were obtained in 40 and 79% yield respectively from **9a** and **9d**. Compound **14c** is a known alkaloid isolated from *Anhalonium lewinii*.[25] The structures were derived from the respective ^{1}H-NMR spectra, as exemplified for **14b** in which the presence of the N-formyl group was indicated by two singlets at 8.23 and 8.21 ppm, combined area one proton, resulting from the two possible conformations of the amide.[26] The isopropyl group is observed as two doublets around 1.0 ppm and a septet of very narrow doublets at 2.10 ppm, J = 6.5 and 1.3 Hz. The described desulfurisation worked well for all cyclisation products on which it was applied, product yields generally ranging from 75–80% (Experimental). Concomitant reactions encountered were (i) reduction of a double bond,[27] e.g. reduction of **10a** gave **16** in 91% yield and (ii) hydrolysis of ester functions present in the molecule, e.g. hydrogenolysis of **7a** gave **17** in 65% yield; the same product was obtained upon desulfurisation of **7b** which had been saponified prior to reduction. A range of azacycloalkanes can be obtained by desulfurisation of the appropriate precursor: besides those already mentioned, pyrrolidine **19**, azepine **21a**, azacyclotetradecane **21b** and azacyclopentadecane **21c** were isolated in good to excellent yields. The combined procedures of N-acyliminium aza-Cope rearrangement and Ra Ni treatment therefore is a method of choice for the preparation of *cis*-2,4-disubstituted pyrrolidines.

The desulfurisation of the thiazine derivatives **22**, **24a** and **24b** gave analogous results. In this manner the N-acetylpiperidine **23** and the N-formylpiperidines **25a** and **25b** were obtained.

Finally, the same reaction was also applied to the products without a bridgehead nitrogen, i.e. **26a** and **26b**. Now the N-cyclohexylformamide derivatives **27a**-**27b** were obtained in high yields, although the initial trans-relationship of the phenyl and amino substituents was partially lost because of the concomitant isomerisation. Similarly **29** was obtained from **28**. The ^{1}H-NMR spectra of these compounds again exhibit the characteristic signals mentioned before, e.g. the formyl group of **27b** gives two singlets at 8.08 and 8.05 ppm. Due to the rotational isomerism of the amide group, two absorptions of the N-Me group are observed, at 2.77 and 2.25 ppm; likewise, the NCH benzylic proton in **29** exhibits two sets of signals at 5.32 and 5.10 ppm.[28]

CONCLUSIONS

The most efficient way to effect the conversion of an S containing lactam appears to be direct desulfurisation. In this manner, a variety of ring structures are accessible, some of which could not easily be arrived at using other routes.[29] Moreover, if the cyclisation step leads to a compound with a defined spatial arrangement, this stereochemistry is retained in the final product. Thus overall stereoselective synthesis of heterocycles is possible with this method.

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, XI-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 AE-MS-902 or Varian Mat 711 mass spectrometer. M.ps were determined on a Leitz m.p. microscope, and are uncorrected. Micro-analyses were carried out by TNO, Utrecht, The Netherlands. THF was distilled from $LiAlH_4$ immediately prior to use. All other reagents were used as supplied. Chromatography was performed over silicagel. Dipe = diisopropylether.

Preparation of starting materials

The polycyclic products used as starting compounds in these studies were obtained as follows: for **7a**, **9a**, **9d**, **10a**, **11a**, **12c**, **13a**, **13d**, **20a** and **28** see ref. 2*c*. For compounds **22** and **24** see ref. 2*d*. For compound **18** see ref. 30. The synthesis of other compounds will be published elsewhere.

General procedure for the reduction of thiocarbamates

A THF soln of the thiocarbamate was added dropwise to a cooled suspension of 3–5 equiv of $LiAlH_4$ in THF under N_2. The supply of N_2 was then disconnected and the mixture refluxed for 17 hr. After cooling in ice, water was added (1 ml per g of $LiAlH_4$ used)[31] stirred at room temp for 15 min, cooled, 15% NaOH aq added (1 ml/g $LiAlH_4$), stirred at room temp for 15 min, cooled, sat. Na_2SO_4 aq added (3 ml/g $LiAlH_4$), plus a small quantity of solid Na_2SO_4 and the mixture stirred at room temp for 2 hr. Subsequently, the precipitate was filtered off, washed well with ether and the combined organic fractions concentrated under reduced pressure to afford the crude product. In this manner the following products were obtained.

1,3,4,5,6,10b-*Hexahydro*-1,1-*dimethylisoquinolin*[2,1-c]-*thiazole* **9b**. 0.699 g (3 mmol) **9a** was reduced with 0.285 g (7.5 mmol) $LiAlH_4$. Work-up afforded 0.6292 g of a yellow oil, from which column chromatography gave 0.5544 g of an oil, yield 84%. IR ($CHCl_3$): no prominent peaks. ^{1}H-NMR: 7.3–7.1 (m, 4H, Ph), 4.46–4.13 (AB quartet, J = 9.5 Hz, 2H, SCH_2N), 3.88 (s, 1H, NCH), 3.6–2.65 (m, 4H), 1.76 and 1.10 (s and s, 6H, $2 \times CH_3$). An exact mass determination gave 219.1061; $C_{13}H_{17}NS$ requires 219.10816.

3,3-*Dimethyl*-6-*aza*-*thiatricyclo*[6.3.1.$0^{2,6}$]*dodec*-10-*ene* **10b**. 0.134 g (0.6 mmol) **10a** was reduced with 60 mg (1.6 mmol) $LiAlH_4$ to afford, after column chromatography, 74.6 mg **10b** as an oil, yield 59%. ^{1}H-NMR: 5.9–5.7 (m, 2H, CH=CH), 4.05 and 3.31 (AB quartet, J = 7 Hz, 2H, SCH_2N), 3.24–3.04 (m, 1H, NCH), 2.6–1.2 (m, 8H), 1.47 and 1.38 (s and s,

6H, 2 × CH_3). An exact mass determination, which for $C_{13}H_{19}NS$ would require 209.12381, gave 209.1250.

3,3 - *Dimethyl* - 6 - *aza* - *thiatricyclo*[6.3.1.$0^{2,6}$]*dodecan* - 10 - *ol* **11b**. 0.165 g (0.6 mmol) **11a** was reduced with 0.114 g (3 mmol) $LiAlH_4$ to afford, after column chromatography, 0.070 g **11b** (50%) as an oil, which solidified, m.p. 119–121°. ^{1}H-NMR: 4.95–4.60 (septet, 1H, CHOH), 4.04 and 3.20 (AB quartet, 2H, J = 6 Hz, SCH_2N), 3.1 (m, 1H, NCH), 2.65–1.9 (m, 7H), 1.8–1.1 (m, 4H), 1.57 and 1.44 (s and s, 6H, 2 × CH_3). An exact mass determination gave 227.1341; $C_{12}H_{21}NOS$ requires 227.13437.

4,4 - *Ethylenedioxy* - 7,7 - *dimethyl* - 1 - *aza* - 8 - *thiabicyclo*[4.3.0]*nonane* **12b**. (a) 4,4 - Ethylenedioxy - 7,7 - dimethyl - 1 - aza - 8 - thiabicyclo[4.3.0]nonan - 9 - one (**12a**). 0.56 g (2.18 mmol) **12c**, 10.0 g (0.153 mol) ethylene glycol and 0.1 g *p*-toluenesulfonic acid hydrate were dissolved in 50 ml benzene and refluxed for 42 hr on a Dean Stark water separator. The solvent was then evaporated, the residue taken up in sat. $NaHCO_3$ aq, extracted three times with $CHCl_3$, the combined extracts washed with sat. NaCl aq, dried over $MgSO_4$ and concentrated under reduced pressure to afford 0.5358 g (78%) crystalline **12a**; m.p. 70–71° (from dipe). IR ($CHCl_3$): 1660 cm^{-1} (CO); ^{1}H-NMR: 4.20–3.95 (m, 1H, NCH_2 eq), 3.97 (s, 4H, OCH_2CH_2O), 3.60–3.40 (m, 1H, NCH), 3.10–2.75 (m, 1H, NCH_2 ax), 1.80–1.55 (m, 4H), 1.52 and 1.38 (s and s, 6H, 2 × CH_3). (Found: C, 54.3; H, 7.0; N, 5.8; S, 13.2. Calc for $C_{11}H_{17}NO_3S$ (Mw 243.33): C, 54.30; H, 7.04; N, 5.76; S, 13.18%.)

(b) 0.143 g (0.6 mmol) **12a** was reduced with 57 mg (1.5 mmol) $LiAlH_4$ to afford, after column chromatography, 0.1004 g of an oil (74%), which crystallised upon standing; m.p. 164–166°. ^{1}H-NMR: 4.00 and 3.43 (AB quartet, J = 6 Hz, 2H, SCH_2N), 3.96 (s, 4H, OCH_2CH_2O), 3.17–2.97 (m, 1H, NCH), 2.50–2.10 (m, 2H), 2.00–1.50 (m, 4H), 1.36 and 1.30 (s and s, 6H, 2 × CH_3). (Found: C, 57.5; H, 8.2; N, 6.1; S, 13.8%. $C_{11}H_{19}NO_2S$ (Mw 229.34). Requires: C, 57.61; H, 8.35; N, 6.11; S, 13.98%.)

6,6 - *Ethylenedioxy* - 9,9 - *dimethyl* - 1 - *aza* - 10 - *thiabicyclo*[6.3.0]*undecane* **13b**. (a) 6,6 - Ethylenedioxy - 9,9 - dimethyl - 1 - aza - 10 - thiabicyclo[6.3.0]undecan - 11 - one (**13a**). 0.187 g (0.69 mmol) **13d** was ketalised with 6.0 g (96.7 mmol) ethylene glycol as **12c**. Work-up afforded 203 mg crystalline **13a** (91%); m.p. 181–183° (dipe). IR (KBr): 1650 cm^{-1} (CO); ^{1}H-NMR: 4.1–3.85 (m, 2H, NCH_2 eq and NCH), 3.97 (s, 4H, OCH_2CH_2O), 3.40–3.05 (m, 1H, NCH_2 ax), 2.0–1.5 (m, 8H), 1.46 and 1.31 (s and s, 6H, 2 × CH_3). (Calc for $C_{13}H_{21}NO_3S$ (Mw 271.38): C, 57.54; H, 7.80; N, 5.16; S, 11.82%. Found: C, 57.6; H, 7.8; N, 5.1; S, 11.6%.)

(b) 51 mg (0.188 mmol) **13a** was reduced with 35 mg (0.92 mmol) $LiAlH_4$. Work-up afforded 40 mg of a yellow oil, which solidified upon addition of EtOH; m.p. 77–79°; yield 83%. ^{1}H-NMR: 4.26 and 3.99 (AB quartet, J = 9 Hz, 2H, SCH_2H), 3.95 (m, 4H, OCH_2CH_2OH), 3.4–3.0 (m, 1H, NCH_2), 2.93 (d of d, 1H, NCH), 2.85–2.50 (m, 1H, NCH_2), 2.4–1.25 (m, 8H), 1.40 and 1.31 (s and s, 6H, 2 × CH_3). (Found: C, 60.3; H, 9.0; N, 5.4; S, 12.4%. $C_{13}H_{23}NO_2S$ (Mw 257.40). Requires: C, 60.66; H, 9.00; N, 5.44; S, 12.46%.) In addition, an exact mass determination gave 257.1454, while 257.1449 would be required.

5 - *Ethyl* - 4 - *hydroxy* - 7,7 - *dimethyl* - 1 - *aza* - 8 - *thiabicyclo*[4.3.0]*nonan* - 9 - *one* **7b**. To a cooled (−78°) soln of 1 mmol DIBAH in 5 ml toluene under N_2 was added 0.0514 g (0.2 mmol) **7a** in 4 ml toluene. The stirred soln was allowed to warm overnight. The mixture was then cooled in ice, 2 ml sat. Na_2SO_4 aq added, stirred at room temp for 3 hr, filtered, the residue washed with ether, the combined organic layers dried over $MgSO_4$ and the solvent evaporated under reduced pressure to afford an oil from which after dipe-crystallisation 30 mg (66%) **7b** was obtained as a white solid; m.p. 162–163° (from dipe/EtOAc). IR ($CHCl_3$): 3440 cm^{-1} (OH); 1655 cm^{-1} (CO); ^{1}H-NMR: 4.40–4.10 (m, 1H, NCH_2 eq), 4.05–3.80 (m, 1H, CHOH), 3.13 (d, 1H, NCH), 2.95–2.60 (m, 1H, NCH_2 ax), 2.30 (br m, 1H, disappears with D_2O, OH), 2.1–1.6 (m, 5H), 1.61 and 1.51 (s and s, 6H, 2 × CH_3), 1.09 (t, 3H, CH_3). (Found: C, 57.6; H, 8.4; N, 6.2; S, 14.1%. $C_{11}H_{19}NO_2S$ (Mw 229.23). Requires: C, 57.62; H, 8.35; N, 6.11; S, 13.96.)

1,2,3,4 - *Tetrahydro* - 1 - *isopropyl* - 2 - *methylisoquinoline* **14a**. 0.102 g (0.47 mmol) **9b** was mixed with a suspension of *ca.* 0.25 Raney nickel (dried by repeated flushing with THF) in 5 ml THF, and refluxed for 18 hr. The mixture was then filtered over Celite, and the filtrate concentrated under reduced pressure to afford 60.6 mg of an oil which, according to its spectral data, was **14a** (yield 69%); ^{1}H-NMR: 7.25–6.95 (m, 4H, Ph), 3.3–2.5 (m, 5H), 2.45 (s, 3H, NCH_3), 1.95 (septet, 1H, $CH(CH_3)_2$), 1.0 and 0.85 (2d, 6H, 2 × CH_3).

1,3,4,5,5,10b - *Hexahydro* - 1,1 - *dimethylisoquinoline*[2,1-c] - *thiazole* - 2,2,2,3 - *trione* **9c**. 0.475 g (2.04 mmol) **9a** was dissolved in 50 ml HCOOH and 5 ml (± 50 mmol) 35% H_2O_2 added dropwise, and the soln stirred at room temp for 18 hr. The solvent was then evaporated under reduced pressure, and the residue recrystallised from EtOH to afford 469 mg (87%) **9c**; m.p. 196–198°. IR (KBr): 1670 cm^{-1} (CO); 1310 and 1150 cm^{-1} (SO_2); ^{1}H-NMR (d-acetone): 4.5 (m, 1H), 3.5–2.8 (m, 8H), 1.91 and 1.04 (s and s, 6H, 2 × CH_3). (Found: C, 58.7; H, 5.8; N, 5.2; S, 12.0%. $C_{13}H_{15}NO_3S$ (Mw 265.33). Requires: C, 58.85; H, 5.70; N, 5.28; S, 12.08%.)

5 - *Ethyl* - 4 - *formyloxy* - 7,7 - *dimethyl* - 1 - *aza* - 8 - *thiabicyclo*[4.3.0]*nonane* - 8,8,9 - *trione* **7c**. 530 mg **7b** was oxidised with H_2O_2 as above, producing 520 mg (87%) crystalline **7c**, which was also produced as follows: 0.103 g (0.4 mmol) **7a** was dissolved in 15 ml $CHCl_3$, 240 mg 85% *m*CPBA (1.2 mmol) in 15 ml $CHCl_3$ added, and the resulting mixture stirred at room temp for 17 hr. The solvent was then evaporated and the residue recrystallised from EtOH–$CHCl_3$ 5:1 to afford 99 mg (86%) crystalline **7c**; m.p. 247–249°. IR (KBr): 1715 cm^{-1} (CO); 1305 and 1170 cm^{-1} (SO_2); ^{1}H-NMR (d-acetone): 8.17 (s, 1H, OCHO), 5.40–5.10 (m, 1H, CHOCHO), 4.35–4.10 (m, 1H, NCH_2 eq), 3.74 (d, 1H, NCH), 3.35–3.0 (m, 1H, NCH_2 ax), 1.53 (s, 6H, 2 × CH_3), 2.0–1.20 (m, 5H), 1.00 (t, 3H, CH_3). (Found: C, 50.1; H, 6.7; N, 4.7; S, 11%. $C_{12}H_{19}NO_5S$ (Mw 289.35). Requires: C, 49.81; H, 6.62; N, 4.84; S, 11.08%.) The above compound was also produced upon H_2O_2/HCOOH oxidation of **7b** in 59% yield.

5 - *Ethyl* - 4 - *hydroxy* - 7,7 - *dimethyl* - 1 - *aza* - 8 - *thiabicyclo*[4.3.0]*nonane* - 8,8,9 - *tridione* **7d**. Oxidation of 75 mg (0.32 mmol) **7b** with 190 mg (± 0.9 mmol) *m*CPBA as described for **7c** afforded 40 mg **7d** as a white crystalline mass; m.p. 236–238°; yield 47%. IR (KBr): 3280 cm^{-1} (OH); 1680 cm^{-1} (CO); 1310 and 1120 cm^{-1} (SO_2); ^{1}H-NMR (d-acetone/DMSO): 4.20–3.85 (m, 2H, CHOH and NCH_2 eq), 3.60 (d, 1H, NCH), 3.20–2.80 (m, 2H, NCH_2 ax and OH), 1.45 and 1.44 (s and s, 6H, 2 × CH_3), 2.10–1.40 (m, 5H), 1.01 (t, 3H, CH_3). (Found: C, 50.5; H, 7.5; N, 5.4; S, 12.2%. $C_{11}H_{19}NO_4S$ (Mw 261.34). Requires: C, 50.56; H, 7.33; N, 5.36; S, 12.27%.)

9,9 - *Dimethyl* - 1 - *aza* - 10 - *thiabicyclo*[6.3.0]*undecane* - 6,10,10,11 - *tetrone* **13c**. 40 mg (0.148 mmol) **13a** was oxidised with H_2O_2 as described for **7c**. Work-up afforded 27 mg **13c** (70%) as a white crystalline mass; m.p. 225–226.5°. IR (KBr): 1720 and 1700 cm^{-1} (CO); 1310 and 1120 cm^{-1} (SO_2); ^{1}H-NMR: 4.10–3.85 (d of m, 1H, NCH_2 eq), 3.55 (d, 1H, NCH), 3.60–3.20 (m, 1H, NCH_2 ax), 2.80–2.25 (m, 4H), 2.0–1.25 (m, 4H), 1.49 and 1.42 (s and s, 6H, 2 × CH_3). (Found: C, 51.2; H, 6.7; N, 5.3; S, 12.2%. $C_{11}H_{17}NO_4S$ (Mw 259.32). Requires: C, 50.95; H, 6.61; N, 5.40; S, 12.36%.)

General procedure for the desulfurisation reaction

The substrate was dissolved in EtOH, Raney nickel slurry added (10- to 20-fold excess by wt) with some more EtOH (total *ca.* 30–50 ml) and the mixture refluxed for 6 hr. The soln was then cooled, filtered over Celite, the filtrate washed thoroughly with CH_2Cl_2 and the combined washings dried over $MgSO_4$ and concentrated under reduced pressure to afford the crude product. In this way, the following compounds were prepared.

4,4 - *Ethylenedioxy* - 1 - *formyl* - 2 - *isopropylpiperidine* **15a**. Reduction of 72.7 mg (0.3 mmol) **12a** afforded 45.5 mg **15a** as an oil after purification by column chromatography; yield 71%. IR ($CHCl_3$): 1660 cm^{-1} (CO); ^{1}H-NMR: 8.11 and 8.03 (2 s, total area 1H, CHO), 4.48–3.85 (m, 1.5 H, NCH deshielded), 3.99 (s, 4H, OCH_2CH_2O), 3.50–3.0 (m, 1.5H, NCH shielded), 3.0–1.5 (m, 5H), 0.99 and 0.82 (d and d, 6H, 2 × CH_3). An exact

mass determination gave 213.1371; $C_{11}H_{19}NO_3$ requires 213.13647.

4,4 - *Ethylenedioxyl* - 1 - *formyl* - 2 - *isopropylperhydro-azocine* **15b**. Hydrogenolysis of 0.0582 g (0.215 mmol) **12c** afforded, after column chromatography, 42 mg **15b** as an oil; yield 81%. IR ($CHCl_3$): 1660 cm^{-1} (CO); ^{1}H-NMR: 8.25 and 7.94 (2s, total area 1H, CHO), 4.0–3.75 (m, 5H, NCH deshielded and OCH_2CH_2O), 3.22 and 2.76 (2m, 2H, NCH shielded), 2.15–1.25 (m, 9H), 0.91 and 0.77 (2d, 6H, 2 × CH_3). An exact mass determination gave 241.1696; $C_{13}H_{23}NO_3$ requires 241.16777.

2 - *Formyl* - 1,2,3,4 - *tetrahydro* - 2 - *isopropylisoquinoline* **14b**. 0.170 g (0.73 mmol) **9a** was reduced to afford 131 mg of a slightly coloured oil which was chromatographed to give 59 mg (40%) of a clear oil with essentially the same spectral data: IR ($CHCl_3$): 1660 cm^{-1} (CO); ^{1}H-NMR: 823 and 8.21 (2s, total area 1H, CHO), 7.3–7.0 (m, 4H, Ph), 4.40–4.05 (m, 1.5H, NCH deshielded, 3.75–3.2 (m, 1.5H, NCH shielded), 2.92 (t, 2H, $PhCH_2$), 2.10 (septet, 1H, $CH(CH_3)_2$), 1.0 and 0.93 (2d, 6H, 2 × CH_3). An exact mass determination gave 203.1292; $C_{13}H_{17}NO$ requires 203.1310.

2 - *Formyl* - 1,1,3,4 - *tetrahydro* - 6,7,8 - *trimethoxy* - 1 - *methylisoquinoline* **14c**. 98 mg (0.33 mmol) **9d** was reduced, affording 69.4 mg of a clear oil (79%) which solidified upon cooling; m.p. 85–88°. IR ($CHCl_3$): 1660 cm^{-1} (CO); ^{1}H-NMR: 8.28 and 8.09 (2s, total area 1H, CHO), 6.41 (s, 1H, Ph), 5.5 and 4.8 (2q, total 1H, PhCHN), 4.36 and 3.17 (2 × q of d, total 1H, NCH), 3.92, 4.81 and 4.80 (3s, 9H, 3 × OCH_3), 3.48 (m, 1H, NCH), 2.95–2.6 (m, 2H, $PhCH_2$), 0.96 and 0.89 (2d, total 3H, CH_3). An exact mass determination gave 265.1307; $C_{14}H_{19}NO_4$ requires 265.13138.

3 - *Formyl* - 2 - *isopropyl* - 3 - *azabicyclo*[3.3.1]*nonane* **16**. Reduction of 0.1766 g (0.79 mmol) **10a** afforded 0.1410 g **16** as a pale yellow oil; yield 91%. ^{1}H-NMR: 8.14 (br s, 1H, CHO), 4.48 (d of m, 1H, NCH deshielded), 3.2–2.65 (m, 2H, NCH shielded), 2.5–1.2 (m, 11H), 1.05 and 0.95 (2d, 6H, 2 × CH_3).

3 - *Ethyl* - 1 - *formyl* - 2 - *isopropylpiperidin* - 4 - *ol* **17**. 0.1264 g (0.49 mmol) **7a** was reduced to afford, after chromatography, 64 mg (65%) **17** as an oil. IR ($CHCl_3$): 3340 cm^{-1} (OH); 1655 cm^{-1} (CO); ^{1}H-NMR: 8.06 and 8.05 (2s, total area 1H, CHO), 4.25–2.3 (m, 6H, 5H upon addition of D_2O), 1.9–1.4 (m, 5H), 1.10 and 1.04 (2d, 6H, 2 × CH_3), 0.86 (t, 3H, CH_3). An exact mass determination gave 199.1567; $C_{11}H_{21}NO_2$ requires 199.15721. The same compound was produced in 46% yield upon treatment of **7b**.

1 - *Formyl* - 4 - (1 - *hydroxy* - 1 - *methylethyl*) - 2 - *isopropylpyrrolidine* **19**. 0.3115 g (1.21 mmol) **18** was reduced to afford 0.2183 g (88%) **19** as an oil which solidified upon cooling; m.p. 76–80° (from dipe EtOH). IR (KBr): 3380 cm^{-1} (OH); 1650 cm^{-1} (CO); 8.25 and 8.19 (2s, total area 1H, CHO), 4.15–3.55 (m, 2H, NCH deshielded), 3.23 and 2.97 (2m, total area 1H, NCH shielded), 2.5–1.5 (m, 5H), 1.26 (s, 6H, 2 × CH_3), 0.94 and 0.87 (2d of d, 6H, 2 × CH_3). An exact mass determination gave 199.1587; $C_{11}H_{21}NO_2$ requires 199.15721.

1 - *Formyl* - 4 - *hydroxy* - 2 - *isopropylperhydroazepine* **21a**. Reduction of 0.1069 g (0.44 mmol) **20a** and subsequent purification by column chromatography afforded **21a** as an oil; yield 73%. IR ($CHCl_3$): 3420 cm^{-1} (OH); 1660 cm^{-1} (CO); ^{1}H-NMR: 8.16 and 7.97 (2s, total area 1H, CHO), 4.25–3.0 (m, 3H), 2.75–1.25 (m, 9H), 0.96 and 0.86 (2d, 6H, 2 × CH_3). An exact mass determination gave 185.1407; $C_{10}H_{19}NO_2$ requires 185.14156.

1 - *Formyl* - 2 - *isopropyl* - 1 - *azacyclotridecan* - 4 - *ol* **21b**. Reduction of 241 mg (0.74 mmol) **20b** afforded 0.1499 g **21b** as an oil; yield 76%. IR ($CHCl_3$): 3420 cm^{-1} (OH); 1660 cm^{-1} (CO); ^{1}H-NMR: 8.10 and 8.00 (2s, total area 1H, CHO), 3.8–2.9 (m, 5H, CHOH and NCH), 1.88 (septet, J = 7 Hz, 1H, $CH(CH_3)_2$), 1.8–1.1 (m, 18H), 0.90 (d, J = 7 Hz, 6H, 2 × CH_3). The mass spectrum showed a peak at *m/e* 268 as the highest value, though too small to be accurately determined ((M − 1)$^+$).

1 - *Formyl* - 2 - *isopropyl* - 1 - *azacyclopentadecan* - 4 - *one* **21c**. 0.110 g (34 mmol) **20c** was desulfurised to afford 98 mg of a brown oil, the ^{1}H-NMR spectrum of which was essentially identical to that of the purified material; yield 23 mg, 23%. IR ($CHCl_3$): 1710, 1680 cm^{-1} (CO); ^{1}H-NMR (C_6D_6): 8.00 and 7.91 (s and s, total area 1H, CHO), 3.4–2.35 (m, 3H, NCH), 1.6–0.7 (m, 23H), 0.79 and 0.56 (2d, 6H, 2 × CH_3). An exact mass determination gave 295.2531; $C_{18}H_{33}NO_2$ requires 295.25111.

1 - *Acetyl* - 2,4 - *dimethylpiperidin* - 4 - *ol* **23**. 72.1 mg (0.32 mmol) **22** was reduced to afford 0.485 g (90%) **23** as an oil. ^{1}H-NMR: 4.7–3.8 (m, 2H), 3.45–2.75 (m, 2H), 2.07 (s, 3H, CH_3CO), 1.9–1.5 (m, 4H), 1.35 (s, 3H, CH_3), 1.21 (d, 3H, CH_3). An exact mass determination gave 171.1265; $C_9H_{17}NO_2$ requires 171.12592.

1 - *Formyl* - 2 - (2 - *phenylethyl*) - *piperidin* - 4 - *ol* **25a**. 0.918 g (0.32 mmol) **24a** was reduced to afford 63.3 mg **25a** as an oil; yield 86%. IR ($CHCl_3$): 3430 cm^{-1} (OH); 1660 cm^{-1} (CO); ^{1}H-NMR: 8.11 and 8.04 (2s, total area 1H, CHO), 7.35–7.15 (m, 5H, Ph), 4.4–3.0 (m, 5H), 2.85–1.0 (m, 8H).

3 - *Ethyl* - 1 - *formyl* - 2 - (2 - *phenylethyl*) - *piperidin* - 4 - *ol* **25b**. 0.3623 g (1.14 mmol) **24b** was reduced to afford 150 mg (51%) **25b** as an oil. IR ($CHCl_3$): 3410 cm^{-1} (OH); 1655 cm^{-1} (CO); ^{1}H-NMR: 8.13 and 7.96 (2s, total area 1H, CHO), 7.4–7.05 (m, 5H, Ph), 4.65–4.0 (m, 1.5H, NCH deshielded and CHOH), 3.8–2.9 (m, 2.5H, NCH), 2.8–2.2 (m, 4H), 2.1–1.3 (m, 6H), 0.91 (t, 3H, CH_3). An exact mass determination gave 261.1716; $C_{16}H_{23}NO_2$ requires 261.17286.

N - (5,5 - *Ethylenedioxy* - 2 - *phenylcyclohexyl*) - N - *methylformamide* **27a**. (a) Compound **26a** 0.107 g (0.41 mmol) **26c** was ketalised as **12a** with 0.5 g (8.06 mmol) ethylene glycol to afford 75 mg crystalline **26a**; m.p. 94–96° (from dipe); yield 60%. ^{1}H-NMR: 7.7–7.2 (m, 5H, Ph), 4.20 (d of d, 1H, NCH), 3.98 (s, 4H, OCH_2CH_2O), 2.82 (s, 3H, NCH_3), 2.4–1.5 (m, 6H).

(b) Desulfurisation of **26a**. 45 mg (0.15 mmol) **26a** was desulfurised to afford 28 mg (69%) **27a** as an oil. ^{1}H-NMR: 7.86 and 7.84 (s and s, total area 1H, CHO), 7.5–7.2 (m, 5H, Ph), 4.15–3.95 (m, 1H), 4.03 (s, 4H, OCH_2CH_2O), 3.1–2.5 (m, 2H), 2.67 (s, 3H, NCH_3), 2.5–1.5 (m, 5H). The mass spectrum showed a peak at *m/e* 275 ($C_{16}H_{21}NO_3$), but it proved too small for an exact mass determination.

N - (5 - *Hydroxy* - 2 - *phenylcyclohexyl*) - N - *methylformamide* **27b**. 77.6 mg (0.266 mmol) **26b** was reduced to afford 0.049 g **27b** as an oil, which solidified upon cooling; m.p. 82–85° (from dipe); yield 79%. IR ($CHCl_3$): 3400 cm^{-1} (OH); 1660 cm^{-1} (CO); ^{1}H-NMR: 7.94 and 7.82 (2s, total area 1H, CHO), 7.5–7.0 (m, 5H, Ph), 4.60 (m, 0.5H, NCH deshielded), 3.85–3.0 (m, 2.5H), 2.8–2.55 (m, 1H), 2.69 and 2.23 (2s, total area 3H, NCH_3), 2.2–1.1 (m, 6H). An exact mass determination gave 233.1407; $C_{14}H_{19}NO_2$ requires 233.14157.

N - *methyl* - N - (5,6,7 - *trimethoxy* - 2 - *phenylindan* - 1 - *yl*) - *formamide* **29**. 0.1161 g (0.31 mmol) **28** was reduced to afford 0.0916 g **29** as a pale yellow oil with essentially the same ^{1}H-NMR spectrum as the colourless oil (67.3 mg, 63% yield) obtained after chromatography. IR ($CHCl_3$): 1665 cm^{-1} (CO); ^{1}H-NMR: 8.08 and 8.05 (2s, total area 1H, CHO), 7.45–7.1 (m, 5H, Ph), 6.60 (s, 1H, Ph), 5.32 and 5.10 (2m, 1H, NCH), 3.90, 3.87 and 3.86 (3s, 9H, 3 × OCH_3), 3.7–2.9 (m, 3H), 2.77 and 2.25 (2s, total area 3H, NCH_3). An exact mass determination gave 341.1602; $C_{20}H_{23}NO_4$ requires 341.16268.

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