The synthesis of a new fused heterocyclic system: hexahydro[1,5]oxathiocino[2,3-*b*]pyrazine

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A brief synthesis of the new heterocyclic system of 1,2,3,7,8,10a-hexahydro-6*H*,10*H*-[1,5]oxathiocino[2,3-*b*]pyrazin-10-imine was achieved, starting from piperazin-2-one derivatives and 1,3-dibromopropane.

Keywords: fused 1,5-oxathiocins, fused pyrazines, piperazinones, ring contraction

The heterocyclic system fusing 1,5-oxathiocin with 1,4-diazine rings has hitherto not been described in the literature. The 1,5-oxathiocane ring is known to form in the reaction of diallyl ether with SCl_2.[1] Partially saturated benzo-fused 1,5-oxathiocines have been obtained in the cyclisation of chloroalkoxybenzylisothiuronium chlorides[2] and, more recently, made from thioketones in intramolecular ene reactions.[3] A thioannulation process of some pyran derivatives was involved in the synthesis of a fully saturated fused system containing the 1,5-oxathiocane moiety.[4] Some 1,5-oxathiocine derivatives have applications in industry as additives in polymerisation processes and in the preparation of some dental materials.[5] Moreover, this system has been postulated as an important intermediate product in photochemical processes leading to macrocyclic natural products.[6]

Results and discussion

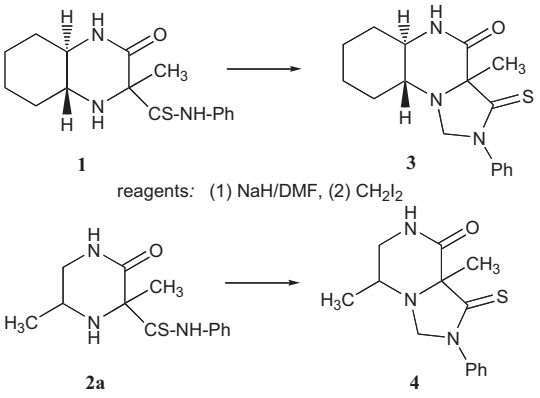
We have recently reported that some saturated 1,4-diazines such as the derivatives of quinoxaline (**1**) and piperazine (**2**) are very useful building blocks in heterocyclisations with diiodomethane, leading to the fused imidazo[1,5-*a*]-quinoxaline and imidazo[1,5-*a*]pyrazine systems **3** and **4** respectively (Scheme 1).[7]

As a sequel to this study we investigated the reaction of the 1,4-diazines **1, 2a** and **2b** with 1,3-dibromopropane. We surmised that cyclisations analogous to those in Scheme 1 would furnish larger-sized ring systems. When piperazine derivatives **2a** and **2b** were used, the reaction unexpectedly proceeded by electrophilic attack of the alkylating agents on the sulfur atom of the thioamide moiety and the oxygen atom of the carbonyl group. As a result, the *N*-phenyl-1,2,3,7,8,10a-hexahydro-6*H*,10*H*-[1,5]oxathiocino[2,3-*b*]pyrazin-10-imines **5a**, **5b** were formed (Scheme 2).

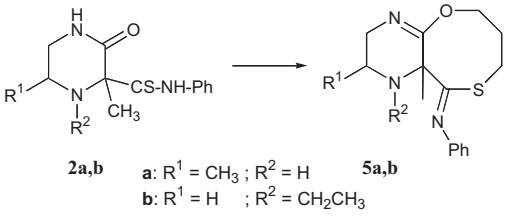
The structures of **5a** and **5b** were deduced from their spectra, in particular their ^{13}C NMR, and from X-ray analysis of **5a**. The latter revealed a highly puckered ring system (see Fig. 1, showing the crystallographic numbering) consisting of an eight-membered (C_6OS) ring condensed with a six-membered (C_4N_2). The latter ring has a slightly twisted sofa conformation, while the eight-membered one has a more complicated conformation, somewhat resembling a chair. Its irregular form may result from the presence of two heteroatoms (S, O) resulting in rather diversified bond lengths and angles.

In contrast to the above, ring closure by bielectrophilic attack of 1,3-dibromopropane on the perhydroquinoxaline **1** leads to the precedented[7] ring contraction to a perhydrobenzimidazole and formation of the thiazine ring in **6** (Scheme 3).

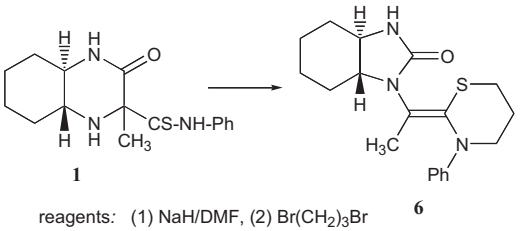
In mechanistic terms, this route shows similarities with the one described in the previous paper,[7] in which the structure of the rearranged product was confirmed by X-ray analysis. The electrophilic attack takes place exclusively at



Scheme 1



Scheme 2



Scheme 3

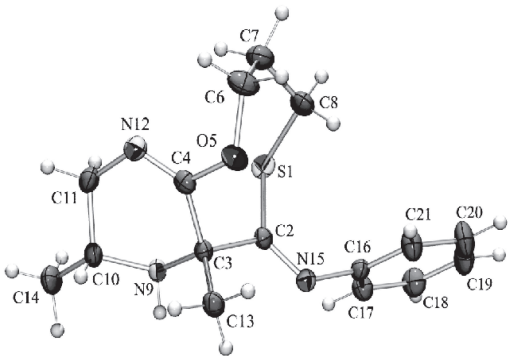


Fig. 1 X–ray of structure **5a**

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the sulfur and the nitrogen atoms of the thioamide fragment of **1**. A sigmatropic rearrangement leads to ring contraction of the 1,4-diazine (perhydroquinoxaline) to a 1,3-diazine (perhydrobenzimidazole) with the formation of the thiazine ring from the thioanilide fragment.

Conclusion

The 1,2,3,7,8,10a-hexahydro-6*H*,10*H*-[1,5]oxathiocino[2,3-*b*] pyrazin-10-imine system, a novel, stable fused heterocyclic system, is obtained according to our methodology from easily prepared piperazine derivatives **2**.[8] The saturated ring-fused analogue **1** follows a different pathway, instead forming a rearranged product (**6**) with perhydrobenzimidazolone and 1,3-thiazine moieties, by a pathway analogous to that demonstrated in our earlier work.[7]

Experimental

Melting points were determined on an electrothermal IA9000 digital melting point apparatus. The IR spectra were obtained on a Bruker IFS 48 spectrometer at room temperature. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AMX 500 NMR spectrometer using TMS as internal standard. Chemical shifts are reported in ppm downfield from TMS. Yields are given for pure products.

Preparation of hexahydro[1,5]oxathiocino[2,3-b]pyrazinimines (**5a**, **b**) The piperazinone (**2a** or **2b)** (2.2 mmol) was stirred for 1 hour in DMF (30 ml) with NaH (0.12 g, 5.0 mmol). 1,3-Dibromopropane (0.34 ml, 3.3 mmol) was added and the solution was heated for 10 hours at 100°C with constant stirring. The solvent was removed under reduced pressure and the residue was washed with a small amount of water, dissolved in acetone, and dried with magnesium sulfate. After removal of the solvent the residue was purified by column chromatography on Al_2O_3 using a CCl_4/acetone 10 : 1 mixture. The final product was isolated using cyclohexane/ethylene chloride 1 : 1 mixture.

2,10a-Dimethyl-N(10)-phenyl-1,2,3,7,8,10a-hexahydro-6H,10H-[1,5]oxathiocino[2,3-b]pyrazin-10-imine (**5a**): Colourless crystals, yield 0.12 g (18%), m.p. 163–165°C. IR (KBr): 3430, 1695, 1626 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.32 (t, 2H, Ph), 7.09 (t, 1H, Ph, J = 7.5 Hz), 6.78 (d, 2H, Ph, J = 7.5 Hz), 4.90–4.94 (m, 1H, CH_2O), 3.78–3.84 (m, 1H, CH_2O), 3.60 (dd, 1H, CH_2N, J = 15.5 and 3.0 Hz), 3.24 (dd, 1H, CH_2N, J = 15.5 and 10.0 Hz), 3.12–3.19 (m, 1H, CH), 2.83 (dd, 1H, CH_2S, J = 15.0 and 8 Hz), 2.53 (dd, 1H, CH_2S, J = 15.0 and 10.0 Hz), 2.29–2.37 (m, 1H, C–CH_2–C), 1.88–1.95 (m, 1H, C–CH_2–C), 1.72 (s, 3H, CH_3), 1.16 (d, 3H, CH_3, J = 6.0 Hz). ^{13}C NMR ($CDCl_3$): δ 164.8 (C=N), 163.0 (C–O), 149.5, 128.6, 123.8, 119.4 (Ph), 65.5, 64.0 (CH_2O), 54.8 (CH_2N), 43.4 (CH), 31.8 (CH_2S), 29.5 (C–CH_2–C), 21.6 (C–$\underline{C}H_3$), 19.3 (CH–$\underline{C}H_3$). MS (EI): *m/z* (%) 303 (8.5, M^+), 200 (100, M^+ – CNPh), 168 (11.8, M^+ – SCNPh), 127 (62.2, M^+ – SCNPh – C_3H_5). Anal. Calcd for $C_{16}H_{21}N_3OS$: C, 63.34; H, 6.98; N, 13.85. Found: C, 63.25; H, 6.89; N, 13.75%.

1-Ethyl-10a-methyl-N(10)-phenyl-1,2,3,7,8,10a-hexahydro-6H,10H-[1,5]oxathiocino[2,3-b]pyrazin-10-imine (**5b**): Colourless crystals, yield 0.12 g (17%), m.p. 240–241°C. IR (KBr): 3435, 1691, 1630 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.22 (t, 2H, Ph), 6.99 (t, 1H, Ph, J = 7.5 Hz), 6.92 (d, 2H, Ph, J = 7.5 Hz), 4.28 (td, 1H, J = 12.5 and 4.5 Hz), 3.79 (td, 1H, J = 12.5 and 4.5 Hz), 3.06 (d, 1H, J = 10.0 Hz), 2.96 (d, 1H, J = 10.0 Hz), 2.78 (t, 1H, J = 11.5 Hz), 2.42–2.56 (m, 2H), 2.24–2.31 (m, 1H), 1.89–2.03 (m, 2H), 1.63–1.69 (m, 1H), 1.45 (s, 3H, CH_3), 1.13–1.27 (m, 1H), 1.08 (t, 3H, CH_3, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$): δ 168.6 (C=N), 164.8 (C–O), 148.7, 128.8, 123.6, 119.3 (Ph), 74.4, 47.5, 46.1, 43.9, 41.4, 30.5, 23.7, 13.5, 13.5 (C aliphatic). Anal. Calcd for $C_{17}H_{23}N_3OS$: C, 64.32; H, 7.30; N, 13.24. Found: C, 64.28; H, 7.45; N, 13.04%.

Preparation of 1-[1'-(3"-Phenylperhydro-1,3-thiazin-2"-ylideno) ethyl]perhydrobenzimidazol-2-one (**6**): The perhydroquinoxalinone **1** (0.76 g, 2.5 mmol) and NaH (0.18 g, 7.5 mmol) in DMF (25 ml) were stirred for 1 h at room temperature. 1,3–Dibromopropane (0.38 ml, 3.7 mmol) was then added and the mixture was stirred for 5 h at room temperature. The solvent was removed under reduced pressure and the residue was washed with a small amount of water, then dissolved in acetone and dried with magnesium sulfate. After removal of the solvent compound **6** was separated by column chromatography on Al_2O_3 using a CCl_4/acetone 2 : 1 mixture. The product formed colourless crystals (0.24 g, 28%), m.p. 177–178°C. IR (KBr): 3228, 2934, 1688 cm^{-1}. ^{1}H–NMR ($CDCl_3$): δ 7.27 (t, 2H, Ph, J = 8.5 Hz), 7.03 (d, 2H, Ph, J = 8.5 Hz), 6.80 (t, 1H, Ph, J = 8.5 Hz), 4.70 (s, 1H, NH), 3.92–3.83 (m, 1H, CH_2N), 3.64–3.57 (m, 1H, CH_2N), 3.32–3.25 (m, 1H, CH), 3.20–3.14 (m, 1H, CH), 2.76–2.67 (m, 2H, CH_2S), 2.07–1.80 (m, 7H), 1.64 (s, 3H, C–$\underline{C}H_3$), 1.49–1.36 (m, 3H). ^{13}C–NMR ($CDCl_3$): δ 161.4 (C=O), 146.4 (C =C), 137.3, 129.4, 118.7, 115.0 Ph, 114.9 (C =C), 63.6 (CH), 59.3 (CH), 47.8 (CH_2 thiazine ring), 29.6, 28.6, 27.4, 24.1, 24.0 (C aliphatic), 21.9 (C–$\underline{C}H_2$–C thiazine ring), 15.5 (CH_3). MS (EI): *m/z* (%) 343 (32.9, M^+), 203 (100, Me–C =C_4H_6SNPh – H), 178 (12.8). Anal. Calcd for $C_{19}H_{25}N_3OS$: C, 66.44; H, 7.36; N, 12.23. Found: C, 66.61; H, 7.44; N, 12.13%.

Crystal structure determination

Compound **5a** crystallises in the monoclinic system, space group $P2_1/c$, with unit cell parameters a = 12.1605(2), b = 11.5968(1), c = 11.8950(1) Å, β = 107.889(1)°, V = 1596.37(3) Å^3, Z = 4. A total of 3649 independent reflections (R(int) = 0.026) were collected at room temperature on a sample (size 0.3 × 0.25 × 0.07 mm) using KappaCCD (Nonius) diffractometer and MoKα radiation. The structure was solved by direct methods and refined by the full–matrix least–squares method on F^2 using SHELX97 program system. Final R indices for 2913 observed reflections ($I>2\sigma(I)$) were equal $R1$ = 0.039, w$R2$ = 0.093 and $R1$ = 0.053, w$R2$ = 0.101 for all 3649 data. The final difference Fourier map of electron density revealed the largest peak and hole 0.18 and –0.36 eÅ^{-3}, respectively. The structural data have been deposited at the Cambridge Crystallographic Data Centre. These data can be obtained free of charge *via* www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk) under reference number CCDC 604252.

Received 20 September 2006: accepted 3 January 2007
Paper 06/4205

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