Synthesis of a cobalt complex of a pyrano[2,3-*b*]quinoxaline-3,4-dithiolate related to molybdopterin

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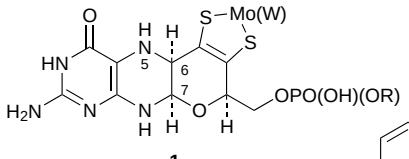
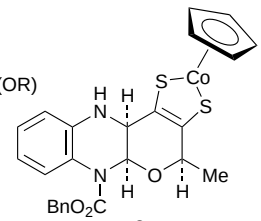
Cobalt complex 2 has been synthesised in which the key features of molybdopterin—a dithiolene ligand on a tetrahydropyrano[2,3-*b*]pyrazine—are modelled.

The pioneering analytical studies on representatives of the oxomolybdoenzymes by Rajagopalan[1] showed the presence of a pteridine (molybdopterin) carrying a C-6 side-chain having two sulfur atoms which ligate molybdenum. X-Ray crystallographic determinations on the oxomolybdoenzymes aldehyde oxidase from *Desulfovibrio gigas*,[2] DMSO reductase from *Rhodobacter sphaeroides* and *R. capsulatus*[3] and formate dehydrogenase from *Escherichia coli*[4] and on the hyperthermophilic tungsten enzyme ferredoxin aldehyde oxidoreductase from *Pyrococcus furiosus*,[5] clearly define the nature of molybdopterin and its mode of ligation to Mo and W **1**. Thus,



1

(R = H or nucleoside)
(other ligands on metal not shown)



2

the metals are chelated by an ene-1,2-dithiolate (dithiolene) which is attached at C-6 to a reduced pteridine ring, as originally proposed by Rajagopalan.[1] However, unsuspected from the degradative and spectroscopic studies of Rajagopalan,[1] all of the protein crystallographic studies observe a tetrahydropyran ring, which can be viewed as resulting from cyclisation of a side-chain hydroxy group to C-7 of a 5,6-dihydropteridine.

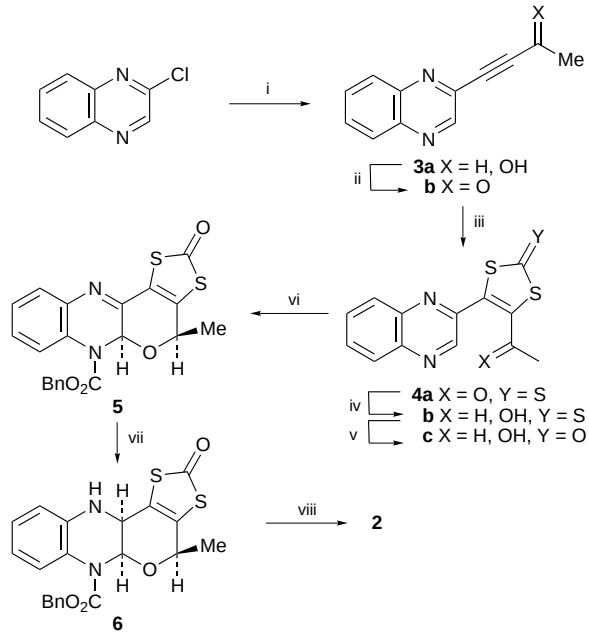
Given the results of these protein crystallographic studies, we have modified our earlier synthetic strategies[6–7] to take account of the presence of the tetrahydropyran ring and herein describe the synthesis of cobalt complex **2** which involves ligation of the metal by a dithiolene moiety linked to pyran and pyrazine rings as identified for molybdopterin.[2–5]

2-Chloroquinoxaline[9] was coupled with but-3-yn-2-ol, without protection of the alcohol, using Pd^0 catalysis, and the product **3a** was oxidised to **3b** following Taylor (Scheme 1).[10] Following precedents,[11] heating the ketone in 4-phenyl-1,3-dithiolane-3-thione[12] at 150 °C gave the 1,3-dithiole-2-thione **4a** in 75% yield. This short route to masked, unsymmetrically substituted dithiolenes has considerable advantages over those we have used earlier.[7,13]

Selective reduction of the ketone functionality with $NaBH_4$ gave alcohol **4b**; conversion to 1,3-dithiol-2-one **4c** was then achieved in high yield with mercury(II) acetate in AcOH at room temperature.

We had shown earlier[14] that treatment of 2-substituted quinoxalines with $NaBH_4$ in the presence of benzyl chloroformate leads to 2-substituted 4-benzyloxycarbonyl-1,2,3,4-tetrahydroquinoxalines, *via* initial *N*-4-acylation then trapping of the resulting quinoxalinium salt by hydride addition at C-7 and finally reduction of the remaining 5,6-imine unit. Therefore, it seemed possible that alcohols such as **4b** and **4c** might react with a chloroformate, in the absence of reductant, to form products in which a first-formed *N*-4-acylquinoxalinium salt has been trapped by an intramolecular nucleophilic attack at C-7 by the side-chain hydroxy group resulting in a cyclisation and giving a pyran ring oriented, with respect to the pyrazine, just as in molybdopterin. We were aware that simple *O*-acylation could compete with these aspirations and indeed, under most of the conditions examined in an extended study of **4b**, *O*-acylation was the only or the predominant reaction observed.

After considerable experimentation it was found that treatment of **4c** with benzyl chloroformate, in the absence of solvent or added base at room temperature, produced the desired cyclisation with no *O*-acylation. Even more rewarding was the finding that one diastereoisomer was formed almost exclusively and that the relative stereochemistry in this tricycle mirrors that in molybdopterin. Thus, **4c** was converted into tetracycle **5** in 90% yield, the relative stereochemistry in **5** being established by the observation of an NOE between the two methine hydrogen signals at δ 6.02 (s) and 4.92 (q, J 6.6) for the BnO_2CN-C*H*OCHMe and MeC*H*OCHNCO_2Bn protons, respectively. Reduction of the remaining imine unit with sodium cyanoborohydride in the presence of AcOH produced only one



Scheme 1 *Reagents and conditions*: i, HC≡CCH(OH)Me, $Pd(OAc)_2$, CuI, Ph_3P, Et_3N (88%); ii, CrO_3, H_2SO_4, Me_2CO, 0 °C (76%); iii, 4-phenyl-1,3-dithiolane-2-thione, 150 °C, N_2 (75%); iv, $NaBH_4$, THF, Pr^iOH, H_2O (69%); v, $Hg(OAc)_2$, Me_2CO, AcOH, room temp. (98%); vi, $ClCO_2Bn$, room temp., N_2 (90%); vii, $NaB(CN)H_3$, AcOH, CH_2Cl_2, MeOH, room temp. (95%); viii, CsOH, MeOH, CH_2Cl_2, room temp., then $Co(Cp)I_2$ (77%).

stereoisomer of the dihydro derivative, shown to have structure **6**, the predicted *cis* relationship of hydrogen atoms at the ring junction being confirmed by an NOE between the protons resonating at δ 5.95 (d, *J* 2.19) ($BnO_2CNCHOCHMe$) and 4.45 (d, *J* 2.19) (NCHCHOCHMe). Thus, this proligand, and the cobalt complex **2** formed from it, possess the same relative stereochemistry at the three chiral centres as in the natural cofactor. Hydrolysis of **6** with aq. CsOH at room temperature produced a solution to which was added cyclopentadienyl (diiodo)cobalt resulting in the formation of purple crystals of **2** in 77% yield, having ^{1}H NMR signals which verified that the organic ligand has been incorporated intact into the metal-containing complex.

We are currently pursuing the application of the methodology described above for the synthesis of molybdopterin, especially to ascertain the chemistry of this biologicaly important ligand. For example, it is not yet established whether the form of molybdopterin identified by protein crystallography represents the catalytically active form. Simple proton-catalysed processes would lead from the structure shown in **1** to forms in which the N–C–O unit has been cleaved, introducing a double bond into the pyrazine ring and allowing electronic communication (*i.e.* conjugation) between the metallocycle and the pteridine unit, and we have speculated on the possible involvement of such interactions in the biological mode of action of these cofactors.[15]

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Notes and References

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