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SYNTHESIS OF 1-(QUINOXALIN-2-YL) -ALKANE-1,2-DITHIOLS AND -ALKENE-1,2-DITHIOLS OF RELEVANCE TO THE MOLYBDOENZYMES COFACTOR, Moco

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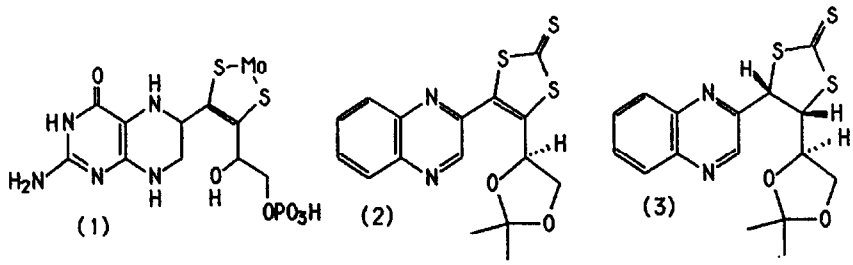
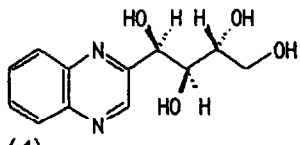
Summary: Syntheses are described of quinoxalines (2) and (3) carrying at C-2 a C_4-side chain, with two sulphur and two oxygen substituents appropriately placed, as model compounds for the pterin which ligands molybdenum in the oxomolybdenum enzymes cofactor, Moco.

The oxomolybdoenzymes, xanthine oxidase, aldehyde oxidase, sulphite oxidase, and nitrate reductase, contain a common cofactor, known as Moco[1]. The organic component of the cofactor is believed, on the basis of chemical degradative and other evidence, to be a 5,6,7,8-tetrahydropteridine, linked *via* C-6 to a four-carbon chain on which are located two sulphur atoms which coordinate molybdenum. A structure (1), with stereochemistry unspecified, has been proposed[2], though the evidence for the dithiolene unit is only circumstantial - that the sulphur atoms may be attached to saturated carbon atoms cannot be discounted. As a contribution to the debate on the structure of Moco, as a model for ultimate total synthetic endeavours, and to produce new ligands suitable for the study of molybdenum-centre-catalysed processes, we report here on the synthesis of the protected diol-ene-1,2-dithiol (2) and diol-dithiol (3), and simpler analogues.



Extensive studies[3] have been made on the quinoxaline side-chain polyols which are produced when *ortho* -phenylenediamine reacts with sugars, under a variety of conditions. Here we have used 2-(D-arabino-tetrahydroxybutyl)quinoxaline[4] (4), which was first reported[4b] one hundred years ago from condensation with glucose, and can be conveniently obtained[4c] using sucrose as the sugar component.

The tetrol (4) was selectively protected (Me_2CO-cH_2SO_4-R.T.)) to produce, as major product, the diol-acetal (5a)[5] [51 %, m.p. 145-46°C]. Mesylation (MesCl-pyridine-R.T.) of (5a) gave an approximately 1:1 mixture of regioisomeric monomesylates (5b) and (5c) (53%) (together with the dimesylate (5d)



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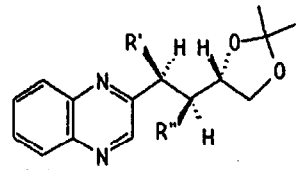
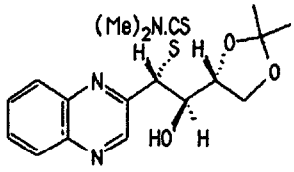


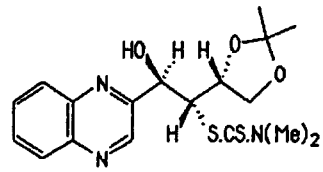
(5)

	R'	R"
a :	OH	OH
b :	OMes	OH
c :	OH	OMes
d :	OMes	OMes

(30%)), which were utilised as an amorphous mixture, after separation from the diester. Reaction with sodium dimethyldithiocarbamate (EtOH-reflux-20 min) gave a mixture of dimethyldithiocarbamates[5] (6a) and (6b). Again without separation, the mixture (6a)/(6b) was successively mesylated and cyclised (MesCl-pyridine-reflux 5 min) and then, without isolation, treated with hydrogen sulphide (RT-1 min) resulting in the production of acetal-trithiocarbonate[5] (3) [amorphous, MH^+, 365.0447 ($C_{16}H_{17}N_2O_2S_3$ requires 365.0452); δ_H ($CDCl_3$) 9.02 (1H, s, quinoxalin-2-yl-H), 8.13 (2H, m, ArH), 7.80 (2H, m, ArH), 5.88 (1H, d, J 2 Hz, C-1'-H), 4.98 (1H, dd, J 2, 10 Hz, C-2'-H), 4.67 (1H, m, C-3'-H), 4.32 (1H, dd, J 6, 9 Hz, C-4'-H), 3.95 (1H, dd, J 4, 9 Hz, C-4'-H), and 1.47 and 1.40 (2 x 3H, 2 x s, $(CH_3)_2C$); m/z (CI) (%) 365 (MH^+, 13), 257 (59), 199 (51), and 169 (46)], acetal-ene-trithiocarbonate[5] (2) [m.p. 162-65°C, M^+, 362.0226 ($C_{16}H_{14}N_2O_2S_3$ requires 362.0217); δ_H ($CDCl_3$) 8.85 (1H, s, quinoxalin-2-yl-H), 8.14 (1H, m, ArH), 8.06 (1H, m, ArH), 7.85 (2H, m, ArH), 5.75 (1H, dd, J 6,7 Hz, C-3'-H), 4.77 (1H, dd, J 7,9 Hz, C-4'-H), 4.13 (1H, dd, J 6,9 Hz, C-4'-H), and 1.59 and 1.44 (2 x 3H, 2 x s, $(CH_3)_2C$); m/z (%) 362 (M^+, 3), 304 (35), 200 (17), 186 (30), 113 (29), 103 (44), and 43 (100)], and, as well, a mixture of the starting mesylates of (6a)/(6b).

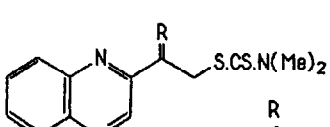


(6a)



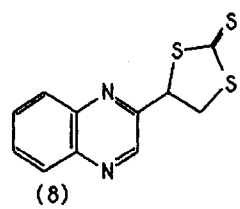
(6b)

In a simpler model series we have demonstrated the efficient conversion of dithiol oxidation level to ene-1,2-dithiol. 2-Dimethylaminothiocarbonylthioacetylquinoxaline[6] (7a) was reduced ($NaBH_4$-MeOH-0°C -> (7b)[5] [87%, m.p. 152-54°C]), then mesylated (MesCl-pyridine-0° ->R.T.) to give (7c)[5]. After 3h at room temperature to complete cyclisation, exposure to a mixture of sodium hydrogen sulphide in aqueous acetic acid at 0°C gave the cyclic trithiocarbonate[5] (8) [67% for the two steps, m.p. 136-38°C].



	R
a :	O
b :	H,OH
c :	H,OMes

(7)



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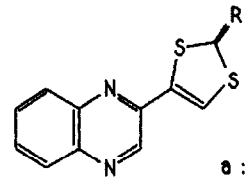
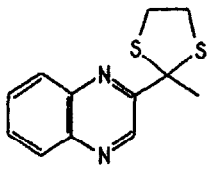


	R
a :	S
b :	O

(9)

Dehydrogenation of (8) could be effected, efficiently on a small scale, by reaction with N-bromosuccinimide (CCl_4-reflux), but this could not be scaled up, however a good yield could be obtained on a larger scale by a Pummerer process (MCPBA-$CHCl_3$-R.T. then $(CF_3CO)_2O$-$CHCl_3$-R.T.) [84%], these alternative routes producing the alkene-1,2-thiol cyclic esters (9b)[5] [m.p. 160-64°C] and (9a)[5] [m.p. 253-54°C] respectively. In analogy to previous work[6] each of these could be easily hydrolysed with base to generate bis-salts of the alkene-1,2-dithiol in solution[7].

In another approach to quinoxalin-2-ylalkene-1,2-dithiolates, 2-acetylquinoxaline[8] was converted ($(CH_2SH)_2$-$BF_3.Et_2O$-$CHCl_3$-R.T.) into the dithioacetal (11) [14%, m.p. 140-42 °C] and thence, by rearrangement[9] (MCPBA-$CHCl_3$/-20°C ->R.T., then $(CF_3CO)_2O$-$CHCl_3$-0°C ->R.T.) into the ene-1,2-dithiol cyclic dithioether (12) [85%, m.p. 135-38 °C; m/z (%) 246 (86, M^+), 218 (100), 189 (14), 174 (56), 129 (31), and 110 (31); δ_H ($CDCl_3$) 8.92 (1H, s, quinoxalin-2-yl-H)), 7.90 (2H, m, 7.65 (2H, m, ArH), 7.37 (1H, s, C:CH), and 3.26 (4H, s, $S(CH_2)_2S$); λ_{max} (EtOH) 227, 258, 295, and 393 nm], it being the plan to selectively cleave[10] the alkyl-sulphur bonds to reveal the desired functionality in (12) or a tetrahydro-derivative (13).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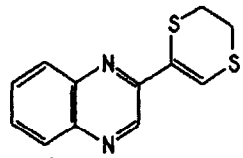
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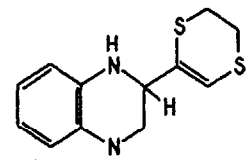
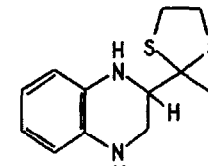
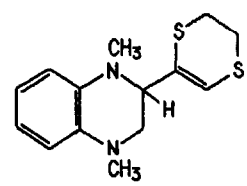

(13)


(14)

Lastly, we report results which are of relevance to the question of the oxidation level of the pyrazine ring in the Moco pteridine: we find, in contrast to an earlier report[11], that sodium borohydride easily reduces the pyrazine ring of simple quinoxalines, for example 2-methylquinoxaline is converted into its 1,2,3,4-tetrahydro-derivative with sodium borohydride in dry methanol at room temperature, and that such simple alkyl-substituted-tetrahydroquinoxalines seem to be relatively stable. However, with side chain functionality, such as that believed to be present in Moco, we find tetrahydroquinoxalines to be **extremely** easily re-aromatised. Thus, although reduction of (12), or of (11), with sodium borohydride did indeed result in the formation of a tetrahydro-derivatives (13) and (14) (MS and NMR) respectively, in which the pyrazine ring alone had been reduced, each reduction product was extremely difficult to handle and each showed a marked tendency to re-aromatise, all spectroscopic measurements revealing a mixture of reduced material and partially or wholly rearomatised species.

(15)



Selective reduction of the hetero-ring and isolation of a stable product at the tetrahydro-oxidation level could be achieved, at the expense of blocking the hetero-ring nitrogen atoms, by treatment of (12) with a reducing agent in the presence of formaldehyde ($NaB(CN)H_3$-aqAcOH-aqCH_2O-R.T.), producing (15)[68%, amorphous, M^+ 278.0912 ($C_{14}H_{18}N_2S_2$ requires 272.0911); δ_H ($CDCl_3$) 6.74(1H, m, ArH), 6.68 (1H, m, ArH), 6.58 (2H, d, J 7 Hz, ArH), 6.06 (1H, s, C:CH(S)), 3.92 (1H, m, tetrahydroquinoxalin-2-yl-H), 3.24 (2H, m, tetrahydroquinoxalin-3-yl-H_2), 3.15 (4H, s, SCH_2CH_2S), and 2.89 and 2.84 (2 x 3H, 2 x s, 2 x CH_3N); m/z (%) 278 (M^+, 66), 161 (100), and 145 (27); λ_{max} (EtOH) 233, 273, and 307 nm].

References

1. J.L.Johnson in "Molybdenum and Molybdenum Containing Enzymes", M.P.Coughlan, Ed., Pergamon Press, Oxford, 1980, pp 345-83.
2. J.L. Johnson, B.E. Hainline, K.V.Rajagopalan, and B.H.Arison, **J.Biol.Chem.**, 1984, 259, 5414; S.P.Cramer, L.P.Solomonson, M.W.W.Adams, and L.E.Mortensen, **J.Am.Chem.Soc.**, 1984, 106, 1467; K.V.Rajagopalan, S.Kramer, and S.Gevdlik, Paper 15, 5th International Conference on Molybdenum Chemistry, 1985; G.N.George, T.R.Hawkes, G.D.Jones, and R.C.Bray, Poster 2.01, *ibid.*
3. For the most recent paper in a series see N.Morita, K.Inoue, and M.Takagi, **Agr.Biol.Chem.**, 1985, 49, 3279.
4. (a) D.Horton and M.J.Miller, **J.Org.Chem.**, 1965, 30, 2457; (b) P.Griess and G. Harrow, **Chem.Ber.**, 1887, 20, 2811 and 2205; (c) S.Gerchakov, P.J.Whitham, and H.P.Schultz, **J.Med.Chem.**, 1966, 9, 266.
5. All new compounds gave satisfactory microanalyses (crystalline) or accurate mass-measured molecular ions (amorphous); other spectroscopic data were in full accord with the structures given; ^1H NMR analysis was of particular relevance to products obtained as regioisomeric mixtures.
6. D.J.Rowe, C.D.Garner, and J.A.Joule, **J.Chem.Soc., Perkin Trans. 1**, 1985, 1907.
7. For metal complex formation from such salts see S.Boyde, C.D.Garner, J.A.Joule, and D.J.Rowe, **J.Chem.Soc., Chem.Commun.**, 1987, 800.
8. G.P.Gardini and F.Minisci, **J.Chem.Soc., C**, 1970,929.
9. For analagous rearrangements see H.Yoshino, Y.Kawazoe, and T.Taguchi, **Synthesis**, 1974, 713; C.H.Chen and B.A.Donatelli, **J.Org.Chem.**, 1976, 41, 3053; N.Ueda, H.Shimizu, T.Kataoka, and M.Hori, **Tetrahedron Lett.**, 1984, 25, 757; C.G.Francisco, R.Freire, R.Hevnandez, J.A.Salazar, and E.Suarez, **ibid.**, 1984, 25, 1621.
10. For comment on the relative ease of reductive cleavage of various types of S-C bonds see J.L.Wardell, Ch. 4, 235 *et seq.*, "The Chemistry of the Thiol Group", Part 1, Ed. S. Patai, 1974, Wiley, London.
11. K.V.Rao and D.Jackman, **J. Heterocycl.Chem.**, 1973,10,213.

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