Model Studies Related to the Cofactor of Oxomolybdoenzymes. Part 4.[1] Reduction of the Pyrazine Ring in Quinoxalines and Pteridines

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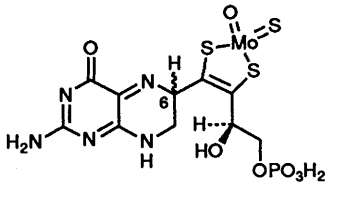
Reduction of quinoxalines and pteridines with sodium borohydride or sodium cyanoborohydride in the presence of benzyl chloroformate gives *N*-benzyloxycarbonyl- or *N,N'*-bisbenzyloxycarbonyl tetrahydro derivatives.

Background

All the oxomolybdoenzymes except nitrogenase, including xanthine oxidase, aldehyde oxidase, sulfite oxidase and nitrate reductase, contain a common cofactor, Moco which has been shown to have molybdenum coordinated *via* two sulfurs in an organic portion which includes a pterin, the complete organic unit being termed molybdopterin. There is evidence[2] that the pyrazine ring in the pterin is in a reduced state, earlier views being that it is at a tetrahydro level but the most recent work[3] suggesting that molybdopterin is a dihydropterin, has a quinonoid tautomeric form, and that therefore partial structure **1** represents Moco. It is relevant to note that a tetrahydropterin is the cofactor for monoamine-synthesising monooxygenases.[4]

The absolute configuration of the side-chain hydroxy-bearing carbon has been deduced to be that shown in **1**, on the basis of a CD comparison between samples of alkyne **2** produced in homochiral form by total synthesis,[5] and by degradation of the enzyme, respectively.[6]



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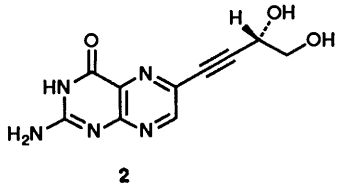

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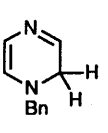
Since it is likely that the mode of action of Moco involves redox processes at the metal centre, possibly linked to changes in the pyrazine ring oxidation level, we have previously reported synthetic studies on quinoxalines carrying 1,2-disulfur-substituted side-chains at C-2,[1,7,8] the complexation[9] of some of these products with molybdenum, tungsten, vanadium and cobalt as models for the situation in Moco, and electrochemical studies[10] on $[Co(\eta^5\text{-}C_5H_5)(S_2CRH)]$ (where R = quinoxalin-2-yl).

Introduction

We showed[11] that it is possible to reduce the pyrazine ring of side-chain substituted quinoxalines chemically to the tetrahydro level, suggested earlier for the pterin in Moco, but that the tetrahydro oxidation level reverts (re-oxidises) readily to the fully aromatic level. We describe here further studies in which regioselective reductions are carried out to produce 1,2,3,4-tetrahydroquinoxalines and 5,6,7,8-tetrahydropteridines, stabilised by (removable) protection in such a way as to facilitate our synthetic work towards molybdopterin and Moco.

Other workers have shown that catalytic reductions[12–14] of pteridines give 5,6,7,8-tetrahydro derivatives, which are oxygen-labile;[13] sodium dithionite treatment leads to 7,8-dihydro derivatives.[15] Acylation of tetrahydropteridines at N-5 produces air-stable compounds,[13] but care is needed, for *N*-5-*ethylation* has been observed under vigorous acetylation conditions.[12]

An elegant method for the partial reduction of pyridines, which also allows isolation of unstable dihydro products in protected/stabilised form, was introduced by Fowler,[16] who found that treatment of pyridine with sodium borohydride in the presence of methyl chloroformate gave a mixture of 1-methoxycarbonyl-1,2- and -1,4-dihydropyridines thus stabilised as urethanes.



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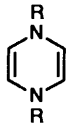


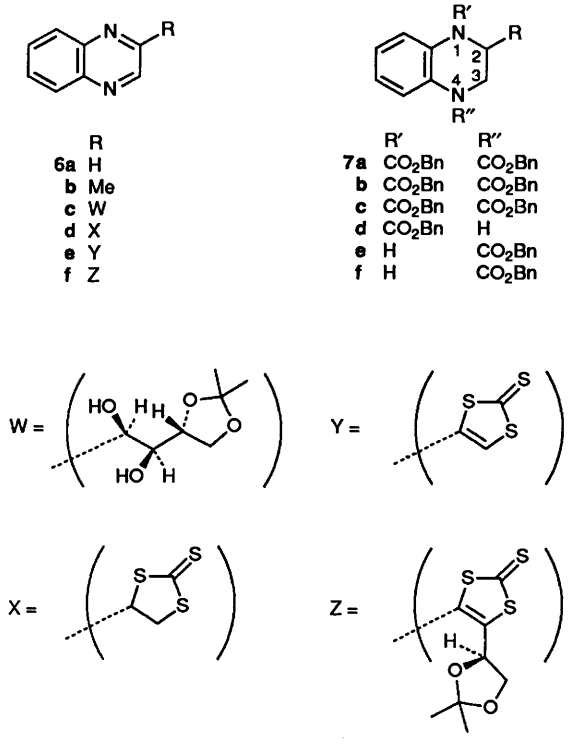
R
4a $SiMe_3$
b CO_2SiMe_3
c COR'
(R' = Me, Ph, Bu^t)

5

N-Benzylpyrazinium iodide has been reduced to the dihydro level, *i.e.* to **3**, using 1-benzyl-4-carbamoyl-1,2-dihydropyridine as reductant.[17] Pyrazine itself, and quinoxaline, have been converted[18] into 1,4-dihydro-1,4-bistrimethylsilyl derivatives **4a** and **5** using a combination of lithium and trimethylsilyl chloride, and **4a**, by further reaction with carbon dioxide, was converted into bisurethane **4b**.[19] Electrolytic reduction of pyrazine in the presence of acylating agents afforded acylated dihydro derivatives **4c**,[20] but electrolytic reduction of quinoxaline followed by attempted trapping with acylating agents led only to polymeric material, though 2-phenyl- and 2,3-diphenylquinoxalines gave 1,4-bis- and 1(4)-mono-methoxycarbonyl-1,4-dihydroquinoxalines.[21] For our synthetic ambitions, we felt that a borohydride-based process would be much more suitable than either metal-based or electrolytic reductions, and would have the added bonus of avoiding the necessity for handling tetrahydropteridines (*vide supra*). The chloroformate–borohydride methodology had not been applied to pyrazines, or fused derivatives such as quinoxalines or pteridines, until we undertook a study[22] of such diazine reduction–protections.

Results

Quinoxalines.—Treatment of quinoxaline **6a** and 2-methylquinoxaline **6b** with sodium borohydride and benzyl chloroformate in methanol at −78 °C produced the expected, doubly protected, tetrahydro derivatives **7a** and **7b**.

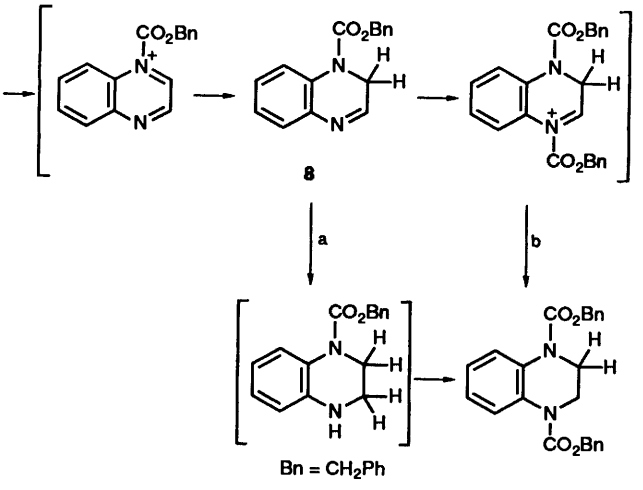


The reduction of the much more complex quinoxalinyl diol acetal **6c**[1] using sodium cyanoborohydride at 0 °C in methylene dichloride also proceeded to give doubly acylated 1,2,3,4-tetrahydro product **7c**, as a *ca.* 1.5:1 (^{1}H NMR) mixture of epimers at the reduced centre C-2.

Comparable reductions, at room temperature, of the three model quinoxalines, **6d–f**,[1,11] carrying sulfur-substituted side chains, produced *mono* acylated tetrahydro derivatives, importantly with no reduction of the 1,3-dithiole-2-thione units in **6e** and **6f**, nor hydrogenolysis of the 1,3-dithiolane-2-thione in **6d**.

The unexpected presence of only one benzyloxycarbonyl moiety in **7d–f** made it necessary to establish the location (1 or 4) of the urethane and this was achieved for **7e** by a single crystal X-ray crystallographic analysis which will be reported in full elsewhere. The reduction product from the other 1,3-dithiole-2-thione-containing quinoxaline, **6f**, is also assigned a structure, **7f**, with the benzyloxycarbonyl group at N-4, on the basis of a comparison of the ^{1}H NMR spectra of the two reduction products. Thus the tetrahydropyrazine ring protons in the spectrum of **7e** were represented by a pair of double doublets at δ 3.85 and 4.10 (CH_2) and a broadened triplet at 4.65 for the methine proton. These compare with double doublets at δ 3.85 and 4.06 and a broadened multiplet at 4.73 for the corresponding protons in **7f**. No such pattern was shown by **7d**, signals for all aliphatic protons, save those for the methylene of the 1,3-dithiolane-2-thione (finely split AB quartet at δ 3.25 and 4.55) and the benzyl group (AB quartet at δ 5.2 and 5.3), being bunched in a tight multiplet centred at δ 3.9, which included the NH. On these grounds we assign structure **7d** to this product, with the urethane located at N-1. It is important to our long term synthetic plans that mono-benzyloxycarbonylation in these complex tetrahydroquinoxalines seemed to be sufficient for their protection against unwanted oxidative rearomatisation; they were stable at room temperature for months.

In considering the mechanistic course of these reductions–protections we envisage initial *N*-acylation then hydride addition producing a cyclic imine, *e.g.* **8** from quinoxaline itself, from which point two possible sequences (Scheme 1) can be



Scheme 1

envisaged: (a) reduction of the imine followed by a second acylation, or (b) interaction of imine nitrogen with a second mol equivalent of chloroformate, then the second hydride reduction. Since we obtained mono acylated products *i.e.* secondary amines failed to react with benzyl chloroformate under the reaction conditions, we suggest that the pathway for formation of the doubly acylated tetrahydro derivatives must involve path (b); it follows then that the formation of mono acylated products, **7d–f**, must involve option (a). Remaining unanswered questions are (a) why does initial acylation of **6d** take place at N-1 where for **6e** and **6f** it must take place at N-4 and (b) why, in the formation of **7d–f**, does the second reduction take place without further intervention by acylating agent.

Pteridines.—Reduction of the simply substituted and protected pteridines **9a–c**, and the more complex tetracetoxy acetamide derivative, **9e**, of 6-(D-*arabino*-tetrahydroxybutyl)-pteridine gave tetrahydro derivatives **10a–c** and **10e**, with *one* added protecting group, located at N-5. The starting point for the assignment of structure to compounds **10** was a single crystal X-ray analysis of **10e**, to be reported in full elsewhere, which showed unequivocally that the benzyloxycarbonyl substituent was located at N-5.

The spectroscopic data for **10b**, the simplest mono-substituted tetrahydro-pteridine studied, unambiguously established its structure. The ^{1}H NMR spectrum showed broadened signals for the C-7-methylene protons, sharpened after D_2O exchange

Table 1 Spectroscopic and analytical data for compounds **7a–f** and **10a–e**

Compd.	Yield (%) (method)	M.p. (°C) (from)	^{1}H NMR[a] ($CDCl_3$) tetrahydroquinoxaline 2-$H_{(2)}$	3-H_2	^{1}H NMR[a] [solvent] tetrahydropteridine 6-$H_{(2)}$	7-H_2	Analyses: found (%)	Formula, requires (%)
7a	52 (A)	105–107 (MeOH)	3.92, s	3.92, s			C, 71.5; H, 5.5; N, 6.9	$C_{24}H_{22}N_2O_4$, C, 71.6; H, 5.5; N, 7.0
7b	57 (A)	76 (hexane)	4.78, m	3.66 and 3.99, 2 × dd, *J* 13, 5			C, 72.2; H, 5.8; N, 6.5	$C_{25}H_{24}N_2O_4$, C, 72.1; H, 5.8; N, 6.7
7c	46 (B)	103–105 (MeOH)	4.90, q *J* 7	3.66, d *J* 7.5			C, 66.2; H, 6.1; N, 4.8	$C_{31}H_{34}N_2O_8$, C, 66.2; H, 6.0; N, 5.0
7d	42 (C)	143–145 (CH_2Cl_2–petroleum)[b]	3.9, m	3.9, m			C, 56.4; H, 4.5; N, 6.8; S, 24.2	$C_{19}H_{18}N_2O_2S_3$, C, 56.7; H, 4.5; N, 7.0; S, 23.9
7e	79 (C)	120–122 (CH_2Cl_2–petroleum)[b]	4.65, t *J* 4	3.85 and 4.10, 2 × dd *J* 14, 5			C, 56.7; H, 4.2; N, 6.9; S, 23.5	$C_{19}H_{16}N_2O_2S_3$, C, 57.0; H, 4.0; N, 7.0; S, 24.0
7f	65 (C)	55–73 decomp. (Et_2O–petroleum)[b]	4.73, m	3.85, dd, *J* 9, 6, 4.06, dd, *J* 12, 3			C, 57.9; H, 5.1; N, 5.8; S, 19.0	$C_{24}H_{24}N_2O_4S_3$, C, 57.6; H, 4.8; N, 5.6; S, 19.2
10a	61 (C)	262–263 (CH_2Cl_2–MeOH)			3.55, s [C_6D_6–$(CD_3)_2SO$]	3.31, s	C, 59.0; H, 6.0; N, 18.0	$C_{19}H_{23}N_5O_4$ C, 59.2; H, 6.0; N, 18.2
10b	37(C)	260–267 decomp. (CH_2Cl_2–Et_2O)			4.7, m [$CDCl_3$]	3.20, d, *J* 12, 3.45, dd *J* 12, 4.5	C, 60.0; H, 6.4; N, 17.5	$C_{20}H_{25}N_5O_4$, C, 60.2; H, 6.3; N, 17.5
10c	78 (C)	288–330 decomp. (MeOH)			4.63, m [$(CD_3)_2SO$]	*ca.* 3.5	C, 60.2; H, 6.8; N, 14.3	$C_{25}H_{33}N_5O_6$, C, 60.1; H, 6.6; N, 14.0
10d	46 (see exptl)	309–310 (EtOH–H_2O)			4.66, m [$(CD_3)_2SO$]	3.27, dd, *J* 12, 4.5, 3.42, d, *J* 12	C, 58.0; H, 6.3; N, 17.0	$C_{20}H_{25}N_5O_5$ C, 57.8; H, 6.0; N, 16.9
10e	65 (C)	248–252 (CH_2Cl_2–Et_2O)			4.59 and 4.66, 2 × br s	3.28–3.42 and 3.60–3.63, 2 × m	C,52.9; H, 5.3; N, 11.2	$C_{28}H_{33}N_5O_{12}$ C, 53.2; H, 5.2; N, 11.1

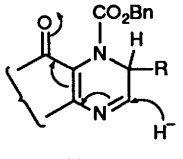
[a] *J*-Values are given in Hz. [b] Petroleum refers to light petroleum (b.p. 40–60 °C).

to a clean AB quartet centred at δ 3.3, *J* 12 Hz, with further fine coupling, *J* 4.5 Hz, of one the two protons to the *one* hydrogen signal at *lower* field, δ 4.7, for the C-6 methine proton. In the spectrum of **10e**, a *ca.* 1:1 mixture of diastereoisomers, the comparable (doubled) signals for ring protons were seen at δ 3.35 and 3.62 (7-H_2) and δ 4.59 and 4.66 (6-H), respectively.

The pivaloyloxy pivalamide, **10c**, and the pivaloate, **10d**, obtained from it by selective hydrolysis of the amide, can be taken together. In the spectrum of the former the C-7-methylene signals were obscured by the water signal, but the C-6-methine signal was again located at lower field, δ 4.63. After amide hydrolysis, both the methine, at δ 4.66, and now the C-7 methylene protons, δ 3.27 and 3.42 could be clearly identified.

Finally, the product from the pyrazine-ring-unsubstituted pterin **9a** could be assigned comparable structure **10a** on the basis of its identical UV absorption to that of the other 5-acyl-5,6,7,8-tetrahydropteridines.

The regiochemistry of acylation and the production of mono-protected tetrahydropteridine derivatives are of intrinsic interest and of relevance to future synthetic work. The sequence must begin with regioselective *N*-5-acylation; this clearly cannot be attributed to the effect of inductive release from a 6-substituent since the same regiochemistry was observed in the unsubstituted situation (**9a** ⟶ **10a**), nor, on the other hand, is this intrinsic reactivity inhibited by the presence of a large 6-substituent (**9e** ⟶ **10e**). A possible explanation is that there is intramolecular delivery to N-5 from an initial 4-carbonyl-O^+-acylated species. A rapid reduction of the residual imine in a reduced intermediate can be related to conjugative stabilisation by the 4-carbonyl, as implied by the arrows on **11**.



11

Experimental

General.—All reagents and solvents were commercial and used without purification unless otherwise stated. Quinoxaline was recrystallised from light petroleum (b.p. 40–60 °C). Dichloromethane was distilled from P_4O_{10} and stored over activated 4 Å molecular sieves, and methanol and pyridine were distilled from CaH_2 and stored over activated 4 Å molecular sieves. Organic solutions were dried over anhydrous magnesium

sulfate and evaporated on a rotary evaporator at temperatures < 50 °C. Silica gel chromatography was effected on Merck Kieselgel 60 or 60H. ^{1}H NMR spectra were measured using a Varian XL300 or a Bruker AC 300 spectrometer. ^{13}C NMR spectra were obtained on Bruker AC 300 or Varian Gemini 200 spectrometers. Analytical and spectroscopic data for new compounds are given in Table 1. *J* values are given in Hz.

Pivalamides **9a**, **9b** *and* **9c**; *Typical procedure for preparation of* 2-*pivaloylaminopteridines*.—A mixture of 6-hydroxymethylpteridine[23] (4.85 g, 25.13 mmol), 4-dimethylaminopyridine (0.46 g, 3.76 mmol), and pivalic anhydride (25 cm^3) was heated under argon at 160–170 °C for 5 h. The excess of anhydride was removed by evaporation under reduced pressure, the residue dissolved in dichloromethane and the solution applied to a pad of silica gel. Elution with dichloromethane–ethyl acetate in a gradient of increasing proportions of 95:5 ⟶ 1:1, and evaporation of the fractions containing product gave crude material which was recrystallised from dichloromethane–diethyl ether to give 6-*pivaloyloxymethyl*-2-*pivaloylaminopteridin*-4(3H)-*one* **9c** (7.08 g, 78%), m.p. 207–208 °C; δ_H($CDCl_3$) 1.27 and 1.25 (2 × 9 H, 2 × s, 2 × Me_3C), 5.43 (2 H, s, CH_2O), 8.39 (1 H, br s, NH), 8.89 (1 H, s, 7-H) and 12.39 (1 H, br s, NH); δ_C($CDCl_3$) 26.67 and 27.14 [2 × $(H_3C)_3C$], 38.85 and 40.53 (2 × Me_3C), 64.67 (CH_2), 130.79 (C-4a), 149.21, 149.39, 150.05 (C-8a, C-6 and C-7), 154.66 (C-2), 159.58 (C-4), and 177.89 and 180.77 (2 × C=O) (Found: C, 56.4; H, 6.6; N, 19.3%. $C_{17}H_{23}N_5O_4$ requires C, 56.5; H, 6.4; N, 19.4%).

Using the same procedure and starting from pterin (114 mg) gave 2-*pivaloylaminopteridin*-4(3H)-*one* **9a** (136 mg, 79%), m.p. 302–306 °C (from CH_2Cl_2–hexane); δ_H($CDCl_3$) 1.35 (9 H, s, Me_3C), 8.39 (1 H, br s, NH), 8.70 (1 H, d, *J* 2, 6-H), 8.84 (1 H, d, *J* 2, 7-H) and 12.38 (1 H, br s, NH); δ_C[$CDCl_3$–$(CD_3)_3SO$] 25.02 [$(H_3C)_3C$], 39.12 (Me_3C), 130.51 (C-4a), 140.97 (C-8a), 148.86, 149.23 (C-6 and C-7), 154.53 (C-2), 158.39 (C-4), and 181.07 (C=O) (Found: C, 53.3; H, 5.4; N, 28.6%. $C_{11}H_{13}N_5O_2$ requires C, 53.4; H, 5.3; N, 28.3%).

Using the same procedure and starting from 6-methylpterin[24] (4.13 g, 23.3 mmol) produced 6-*methyl*-2-*pivaloylaminopteridin*-4(3H)-*one* **9b** (3.56 g, 58%), m.p. 322–335 °C (from MeOH); δ_H($CDCl_3$) 1.33 (9 H, s, Me_3C), 2.74 (3 H, s, Me), 8.37 (1 H, br s, NH), 8.71 (1 H, s, 7-H) and 12.33 (1 H, br s, NH); δ_C($CDCl_3$) 21.63 (Me), 26.94 [$(H_3C)_3C$], 40.46 (Me_3C), 130.84 (C-4a), 148.47, 150.85, 152.90 (C-8a, C-6, C-7), 153.37 (C-2), 159.81 (C-4) and 180.44 (C=O) (Found: C, 55.3; H, 5.9; N, 26.7%. $C_{12}H_{15}N_5O_2$ requires C, 55.2; H, 5.8; N, 26.8%).

2-*Acetylamino*-6-(D-arabino-*tetraacetoxybutyl*)*pteridin*-4-(3H)-*one* **9e**.—6-(D-*arabino*-Tetrahydroxybutyl)pteridin-4-(3*H*)-one[25] (9.78 g, 34.56 mmol), acetic anhydride (80 cm^3), and pyridine (80 cm^3) were heated under argon at 100–110 °C for 2.5 h. Evaporation, addition of acetone (500 cm^3), filtration, removal of solvent, and purification by dry flash chromatography, eluting with chloroform, produced a crude mixture (16.40 g, *ca.* 4:1 by ^{1}H NMR) of regioisomers. Two recrystallisations from CH_2Cl_2–Et_2O afforded the *title compound* **9e** (10.4 g, 61%) free from the 7-isomer, m.p. 121–123 °C, δ_H($CDCl_3$) 1.98, 2.05, 2.14, 2.22 (4 × 3 H, 4 × s, 4 × O_2CMe), 2.49 (3 H, s, NCOMe), 4.24 (2 H, qd, *J* 21, 12, 4 and 3, 4′-H_2), 5.34–5.40 (1 H, m, 3′-H), 5.70 (1 H, dd, *J* 10 and 2, 2′-H), 6.38 (1 H, d, *J* 2, 1′-H), 8.87 (1 H, s, 7-H), 10.51 (1 H, br s, NH) and 12.71 (1 H, br s, NH); δ_C($CDCl_3$) 20.60, 20.75, 20.92 (H_3CCO_2), 25.05 (H_3CCON), 61.72 (C-4′), 68.05 (C-3′), 70.57 (C-2′), 72.07 (C-1′), 130.87 (C-4a), 148.02, 150.00, 150.30, (C-8a, C-6 and C-7), 154.58 (C-2), 159.85 (C-4), 169.75, 169.83, 170.68 (4 × MeCOO) and 174.09 (MeCON) (Found: C, 48.7; H, 4.8; N, 13.9%. $C_{20}H_{23}N_5O_{10}$ requires C, 48.7; H, 4.7; N, 14.2%).

Typical Procedures for Reduction of Quinoxalines and Pteridines.—*Method A*, e.g. *synthesis of* 1,4-*dibenzyloxycarbonyl*-1,2,3,4-*tetrahydroquinoxaline* **7a**. Sodium borohydride (156 mg, 4.12 mmol) and benzyl chloroformate (0.67 cm^3, 4.71 mmol) were added to a solution of quinoxaline (153 mg, 1.18 mmol) in methanol (5 cm^3) stirring at −78 °C under argon. The mixture was allowed to warm to room temperature and after 1 h solvent was removed and the residue partitioned between ethyl acetate and water. The aqueous layer was re-extracted with ethyl acetate and the combined organic extracts were dried, filtered and evaporated to give crude material (377 mg), column chromatography of which (eluting with hexane with increasing amounts of CH_2Cl_2) afforded the *bis-urethane* **7a** (247 mg, 52%).

Method B, e.g. *synthesis of* (4R)-2,2-*dimethyl*-4-[(1S,2R)-1,2-*dihydroxy*-2-(1,4-*dibenzyloxycarbonyl*-1,2,3,4-*tetrahydroquinoxalin*-2-*yl*)*ethyl*]-1,3-*dioxolane* **7c**. Benzyl chloroformate (0.055 cm^3, 0.39 mmol) and sodium cyanoborohydride (26 mg, 0.41 mmol) were added to a stirred solution of the quinoxaline **6c** (105 mg, 0.36 mmol) in dichloromethane (5 cm^3) at 0 °C under argon. After 1 h, second equivalents of benzyl chloroformate (0.055 cm^3) and sodium cyanoborohydride (26 mg) were added and the reaction allowed to warm to room temperature over 16 h. The solvent was removed under reduced pressure and the residue partitioned between ethyl acetate and water. The organic layer was dried, filtered and evaporated leaving an oil (211 mg) which was purified by flash chromatography, with gradient elution using CH_2Cl_2–EtOAc giving material which by crystallisation from methanol gave the *title compound* **7c** (93 mg, 46%) as a white solid shown by ^{1}H NMR to be a mixture of epimers at C-6 (1.5:1).

Method C, e.g. *synthesis of* 5-*benzyloxycarbonyl*-5,6,7,8-*tetrahydro*-2-*pivaloylaminopteridin*-4(3H)-*one* **10a**. Benzyl chloroformate (0.43 cm^3, 3.29 mmol) and, after 0.5 h, sodium cyanoborohydride (222 mg, 3.46 mmol) were added to a solution of the pterin, **9a** (214 mg, 0.87 mmol) in methanol (50 cm^3) under argon at room temperature. After 16 h the solvent was evaporated, the residue washed with hexane (4 × 30 cm^3), dissolved in acetone (50 cm^3), filtered and evaporated to leave a white foam (603 mg), flash chromatographic purification of which ($CHCl_3$–MeOH in a gradient) and recrystallisation from dichloromethane–methanol gave the *title compound* **10a** (203 mg, 61%) as a white solid.

5-*Benzyloxycarbonyl*-6-*pivaloyloxymethyl*-5,6,7,8-*tetrahydropteridin*-4(3H)-*one* **10d**.—The pivalamido pivaloate, **10c** (33 mg, 0.066 mmol) was suspended in a saturated solution of methanolic ammonia (5 cm^3) and the mixture stirred for 16 h. After evaporation, the residue was washed with methanol (10 cm^3), acetone (200 cm^3) and diethyl ether (20 cm^3). Drying to constant weight gave the *pivaloate* **10d** (13 mg, 46%).

Acknowledgements

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References

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