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HYDROGENATION OF SILYLATED PTERIDINES IN BENZENE SOLUTION[1]

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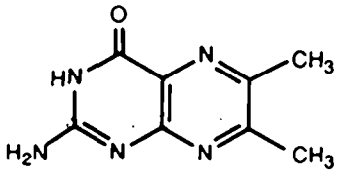
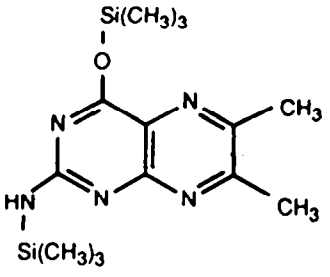
ABSTRACT - Hydrogenation of pteridines in benzene solution was investigated by solubilising them either as their trimethylsilyl or their 4-benzyloxy derivatives. Using a platinum catalyst, 6,7-dimethyl-4-trimethylsiloxy-2-trimethylsilylaminopteridine (2) could be converted to cis-6,7-dimethyl-5,6,7,8-tetrahydropterin (3), provided that the 4-siloxy group was first selectively cleaved by water. The same silylated pteridine, (2), in anhydrous benzene with either Rh(DIOP)Cl or $[Rh(COD)(DIOP)]^+ClO_4^-$, underwent a novel de-silylation reaction to give 6,7-dimethylpterin, (1), with no reduction of the pyrazine ring.

The biologically important pteridine derivatives such as folic acid or biopterin are usually found in nature in their reduced forms. Tetrahydrofolate, for example, is the key coenzyme involved in one-carbon transfer in nature, and tetrahydrobiopterin is currently the subject of much interest because of its association with diseases such as Parkinson's disease. Reduction of the pyrazine ring is thus one of the most important reactions of pteridines, and has been achieved over the years using a wide variety of reducing systems.[2] Amongst these, catalytic hydrogenation remains one of the most useful methods available. Because of the highly insoluble nature of most pteridines, however, catalytic reduction with hydrogen has usually had to be carried out in highly polar solvents such as aqueous acid or trifluoroacetic acid, and this has precluded the use of modern chiral hydrogenation catalysts, which are mostly used in organic solvents. We therefore investigated the hydrogenation of some model pteridine compounds in benzene solution by solubilising them as either 4-benzyloxy or trimethylsilyl derivatives. As well as achieving their reduction in organic solution, we also observed a novel de-silylation reaction, arising from the interaction of a silylated pteridine with a ligand-coordinated rhodium catalyst in benzene solution.

6,7-Dimethylpterin (1) was silylated by refluxing in hexamethyldisilazane containing a catalytic amount of ammonium sulphate. The crude product was purified by sublimation and was obtained as a yellow solid which was extremely sensitive to moisture, being hydrolysed rapidly on exposure to air



(1)



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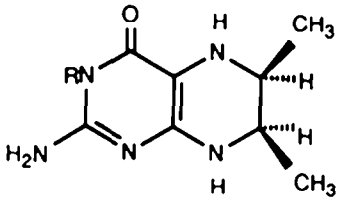
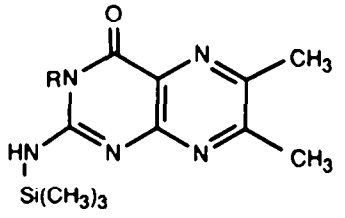


(3) R=H

(4) R=CH_3



(5) R=H

(6) R=CH_3

even for a few minutes. It was stored under nitrogen and used within one week. Its u.v. and ^1H n.m.r. spectra showed it to be the disilyl compound (2). It was also prepared in pyridine solution with hexamethyldisilazane and chlorotrimethyl silane,[3] although this method was found to be less satisfactory. When a solution of this disilyl derivative (2) in dry benzene was stirred under an atmosphere of hydrogen in the presence of a platinum catalyst, no uptake of hydrogen was observed. However, when a small amount of benzene which had been saturated with water was introduced into the reaction mixture, uptake of hydrogen commenced almost immediately, followed by slow precipitation of 6,7-dimethyl-5,6,7,8-tetrahydropterin (3). This compound is extremely susceptible to aerial oxidation, and was therefore isolated as its stable dihydrochloride.[4] It was characterised by its ^1H n.m.r. and u.v. spectra. The u.v. spectrum was measured in 0.1M HCl and exhibited no absorption above 300 nm, confirming that the pyrazine ring of (2) had been reduced. The absorption maxima at 220 and 267 nm corresponded with values reported in the literature[5] for compound (3). The ^1H n.m.r. spectrum of (3) was measured at 80 MHz in 0.5M DCl solution and showed only a six proton triplet at 1.33 p.p.m. and a two proton multiplet at 3.9 p.p.m., assigned respectively to the 6 and 7 methyl groups, and to the 6 and 7 protons. There were no signs of any peaks due to unreacted starting material (1). The 100 MHz n.m.r. spectrum of the 6,7-cis-diastereoisomer of (3) has already been reported by Viscontini and co-workers [6,7] and also by Armarego and Schou,[8] who were able to assign the cis stereochemistry on the basis of the small 6H-7H coupling constant. When measured at 80 MHz, the unresolved multiplet for these protons did not allow their vicinal coupling constants to be extracted from the spectrum. Nevertheless, the chemical shift position and the narrow spread of this multiplet showed that the product (3) obtained by hydrogenation of silyl compound (2) in benzene solution was also cis. This was

confirmed by comparison of it with an authentic sample of cis (3) prepared by hydrogenation of (1) over platinum in trifluoroacetic acid.[4,9]

In the ^{1}H n.m.r. spectrum of (3) as measured in deuterium oxide by us, the signals of the 6- and 7-methyl groups, and also of the 6- and 7-protons, appeared consistently at higher fields (almost 0.5 p.p.m.) than the values reported by other workers,[6,8] also measured in deuterium oxide. This seeming discrepancy turned out to be due to the use of different types of standards. We found that lower δ values (i.e. higher field signals) were obtained when an internal standard of water soluble sodium 2,2,3,3-tetradeuterio-3-(trimethylsilyl)propionate was used, whereas higher δ values were obtained when an external standard of water insoluble tetramethylsilane was used. A similar observation with other pteridines was made by von Philipsborn et al.[10] and low δ values have also been recorded for compound (3) at 60 MHz in deuterium oxide using an internal standard.[11]

We believe that it is the bulky trimethylsiloxy group at the 4 position of (2) which is responsible for the failure of the latter to undergo hydrogenation in the absence of water, and that hydrogenation in the presence of water occurs because of an initial selective hydrolytic cleavage of the 4-O-trimethylsiloxy group. The species actually undergoing hydrogenation would thus be the monosilyl derivative (5), formed in situ in the reaction medium. Evidence supporting this idea was obtained by preparing the monosilylated compound, 3,6,7-trimethyl-2-trimethylsilylamino-4(3H)-pteridinone (6) and hydrogenating it over a platinum catalyst. Absorption of hydrogen occurred immediately without the necessity for addition of any water, and the tetrahydro product (4) was isolated as its hydrochloride. This was reasonably stable in air. However, a solution of it in phosphate buffer at pH 7.1 was smoothly oxidised on standing in air at room temperature to 3,6,7-trimethyl-7,8-dihydro-4(3H)-pteridinone, as shown by following the reaction by u.v. (figure 1). No reaction occurred when a suspension of unsilylated pterin (1) in benzene was stirred under hydrogen with a platinum catalyst.

An attempt was made to prepare 3-methyl-6,7-bis(trideuteromethyl)-pterin from 3,6,7-trimethylpterin by base catalysed exchange in sodium deuteroxide solution. Complete exchange of the 6- and 7- protons was achieved success-

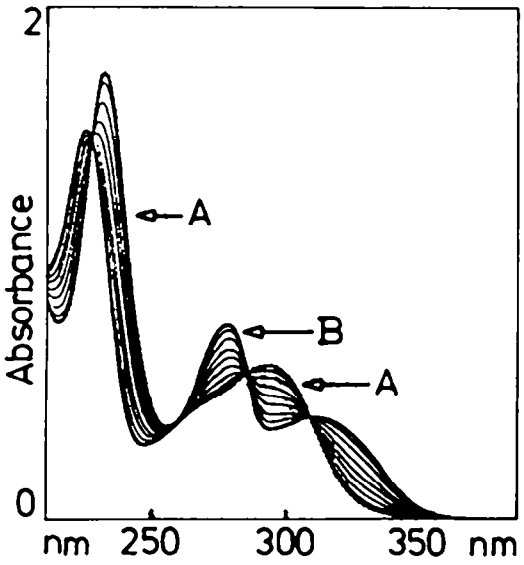
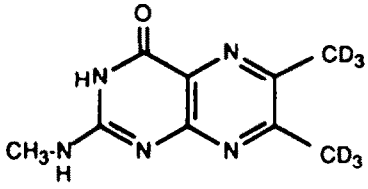


FIGURE 1

A. 3,6,7-trimethyl-5,6,7,8-tetrahydropteridin-4(3H)-one in phosphate buffer, pH 7.1

B. Same solution after standing for 3 hours in air (conversion to 3,6,7-trimethyl-7,8- dihydropteridin-4(3H)-one)

fully. It was not possible to prevent a concomitant Dimroth rearrangement taking place, however, and the product isolated was 2-methylamino-6,7-bis-(trideuteromethyl)-4(3H)-pteridinone (7), as shown by ^1H n.m.r. and u.v. spectroscopy. This was hydrogenated over platinum in trifluoroacetic acid solution [4,9] to give its cis tetrahydro derivative (8), the stereochemistry of which was apparent from its ^1H n.m.r. spectrum, in which the 6- and 7-protons appeared as an AB quartet with coupling constant of 3.3 Hz.



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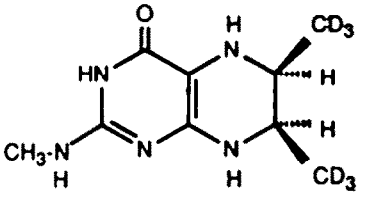
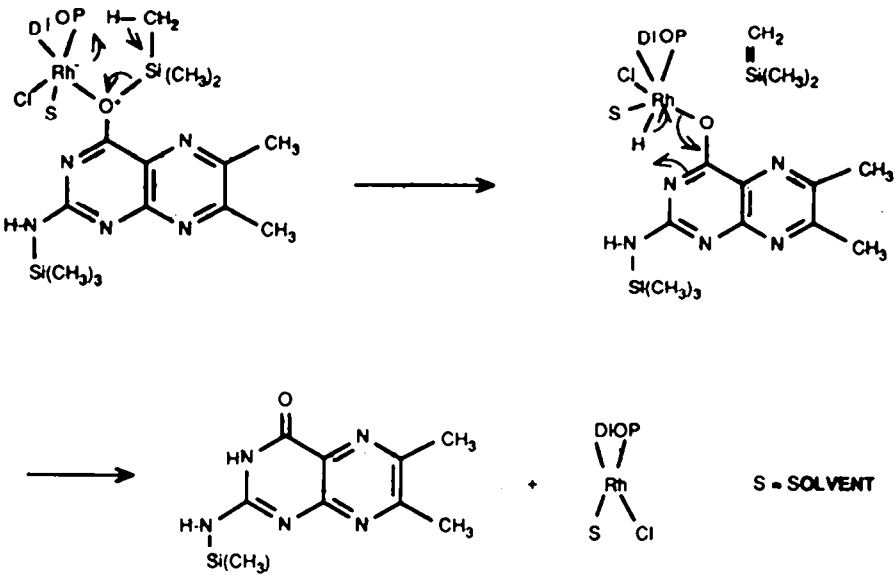


(8)

This successful hydrogenation of the silylated pteridine (2) in benzene solution over a platinum catalyst led us to attempt the homogeneous hydrogenation of (2) using the soluble chiral rhodium catalyst, Rh(DIOP)Cl. We found, however, that no absorption of hydrogen occurred in this system whether water was admitted to the reaction mixture or not, and that instead, the desilylated pterin (1) was precipitated almost quantitatively from solution after a few hours at room temperature. This desilylation did not occur in the absence of catalyst. It was not due to hydrolysis by water in the reaction medium, for it occurred even under the most rigorously anhydrous conditions. Neither was it due to small amounts of free DIOP from the catalyst, since no precipitation occurred when free DIOP was added to a benzene solution of (2). Nucleophilic activity by chloride from the catalyst was also shown to be an unlikely explanation for the desilylation since the same reaction occurred using the cationic catalyst, $[Rh(COD)(DIOP)]^+ClO_4^-$, which contains only the very weakly nucleophilic perchlorate anion. These control experiments suggested, therefore, that the desilylation reaction was due to a direct interaction of the silylated pterin (2) with the catalyst. Furthermore, it was not necessary for the catalyst to be in its dihydrido form, for the reaction occurred even when no hydrogen was admitted to the system. Finally, an immediate precipitation of the desilylated pterin (1) was found to occur when a benzene solution of (2) was added to a solution of the rhodium catalyst containing a few drops of thiophene. This effect was not due to thiophene alone, for no reaction was observed within 24 hours when thiophene was added to a solution of (2) in dry benzene. It is possible that the thiophene, being a better electron donor molecule than benzene, promotes conversion of the catalyst from a bridged dimeric form in benzene solution to a more reactive monomeric form.

The hydrogen atoms necessary for the conversion of (2) into (1) could not have come from water, which was rigorously excluded from the reaction mixture. Neither are they likely to have been derived from the DIOP ligand, nor from solvent molecules. We propose that the necessary hydrogen atoms are derived from the trimethylsilyl groups, and are transferred under the influence of the catalyst. The suggested mechanism (scheme 1) shows coordination of the silylated pteridine (2) to the rhodium atom of the catalyst, followed by intramolecular transfer of hydrogen from a trimethylsilyl group to the metal. This

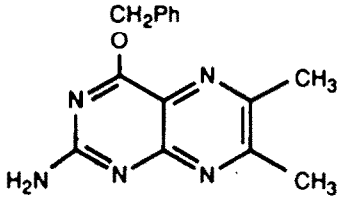


SCHEME 1

involves conversion of the rhodium from oxidation state (I) to oxidation state (III), with the formation of a hexacoordinate complex and the concomitant elimination of the silyl group as a silaethene. In the final step, the hydrogen is transferred back again to N-3 of the pteridine, which simultaneously cleaves from the catalyst and is precipitated. This is a novel mechanism in that the hydrogen atoms on the silyl methyl groups are not in any usual sense "activated". Rhodium(I), however, has been known to abstract completely unactivated hydrogen from an aliphatic group under mild conditions, [12] and oxidative addition reactions of rhodium are, of course, well known.[13] The scheme shows cleavage of an O-silyl residue, but the same mechanism could operate for cleavage of an N-silyl residue. There is now abundant precedent for reactions which are believed to proceed via unstable silene intermediates,[14] and some evidence was obtained in the present reaction showing that the final silicon-containing products were different when desilylation of (2) was effected by interaction with rhodium catalyst rather than by hydrolysis with water. A solution of (2) in hexadeuterobenzene was treated with deuterium oxide, and the precipitated 6,7-dimethylpterin (1) was filtered off. The filtrate, which contained the silyl residues, was examined directly by ^1H n.m.r., when three large high field singlets and one small one were observed at 0.05, 0.35, 0.45, and 0.15 p.p.m. respectively. When the same disilylated pterin (2) in hexadeuterobenzene was treated with $[Rh(COD)(DIOP)]^+ClO_4^-$ catalyst and the precipitate of (1) filtered off as before, the filtrate showed only two high field peaks in the n.m.r., at 0.12 and 0.29 p.p.m., both of these being at different chemical shifts than were the peaks observed in the deuterium oxide experiment.

Folic acid can form a trimethylsilyl derivative in which up to five trimethylsilyl groups may be present. When a benzene solution of silylated folic acid was stirred in a hydrogen atmosphere at room temperature with either of the rhodium catalysts, Rh(DIOP)Cl or $[Rh(COD)(DIOP)]^+ClO_4^-$, no precipitation of

folic acid occurred. This reflects the presence of extra ester and N-10 silyl groups, which could not be cleaved following the mechanism described above, and which would serve to keep the folic acid in solution. No tetrahydrofolate was formed, however, nor was any hydrogen absorbed, even when a solution of water in benzene was added to the hydrogenation mixture. This probably reflects the fact that rhodium complex catalysts are much more sterically demanding than either platinum or palladium catalysts. An alternative method which has been used to solubilise pterins in organic solvents [15] is to convert them into their 4-alkoxy derivatives. We prepared 2-amino-4-benzyloxy-6,7-dimethylpteridine (9) and found that it could also be hydrogenated successfully in benzene solution using a platinum catalyst, to give its tetrahydro derivative, 2-amino-4-benzyloxy-6,7-dimethyl-5,6,7,8-tetrahydropteridine (10). The stereochemistry of (10) could not be ascertained from its p.m.r. spectrum at 80 MHz. It is, perhaps, surprising that the benzyloxy group was not removed by hydrogenolysis under these conditions. In trifluoroacetic acid solution, on the other hand, hydrogenation of (9) over platinum afforded only 6,7-dimethyl-5,6,7,8-tetrahydropterin (3). No reduction occurred when (9) was hydrogenated in benzene solution with the soluble catalyst, $[Rh(DIOP)(COD)]^+ClO_4^-$.



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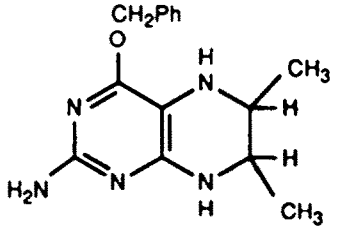

(10)

ABBREVIATIONS:

DIOP = 2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis-(diphenylphosphino)butane
COD = 1,5-cyclooctadiene

ACKNOWLEDGEMENTS

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EXPERIMENTAL

N.m.r. spectra were measured on a Bruker WP-80 instrument, using sodium 2,2,3,3-tetradeutero-3-(trimethylsilyl)propionate as an internal standard in D_2O and DCl solutions, and tetramethylsilane as an internal standard in other solvents. U.v. spectra were recorded on a Pye-Unicam SP8-200 spectrophotometer. Hexamethyldisilazane was obtained from Aldrich Chemical Co. and was distilled before use. Trimethylchlorosilane and rhodium trichloride trihydrate were also obtained from Aldrich. (-)-2,3-O-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino) butane ((-)-DIOP) was obtained from Fluorochem. Benzene used as solvent was purified by shaking it with portions of concentrated sulphuric acid until no further colour appeared in the acid layer. It was then washed several times with aqueous sodium hydrogen carbonate solution, and finally with distilled water. After preliminary drying over anhydrous calcium chloride, the benzene was filtered, and distilled onto sodium wire. It was then refluxed over potassium in a nitrogen atmosphere, and finally distilled from potassium in an atmosphere of nitrogen immediately before use. Air or moisture sensitive compounds were handled either in a glove bag filled with dry nitrogen, or on a vacuum line.

6,7-Dimethyl-4-trimethylsiloxy-2-trimethylsilylaminopteridine (2).
Method A. A suspension of 6,7-dimethylpterin (1) (100 mg) in redistilled hexamethyldisilazane (20 ml) containing a few crystals of ammonium sulphate was refluxed until a clear solution was obtained. Excess hexamethyldisilazane was removed by distillation in a stream of dry nitrogen, and the remaining brown solid sublimed at 180° at 10^{-4} mm Hg using a vacuum line. The sublimed 6,7-dimethyl-4-trimethylsiloxy-2-trimethylsilylaminopteridine (2), (140 mg; 80%) was obtained as a pale yellow solid, and was stored under nitrogen and used within one week. $\lambda_{max.}$ (cyclohexane) 239, 267, 358 nm ; δ_H (C_6D_6) 0.60 (9H, s, $Si(CH_3)_3$), 0.65 (9H, s, $Si(CH_3)_3$), 2.40 (6H, s, $2xCH_3$); δ_H ($CDCl_3$) 0.50 (9H, s, $Si(CH_3)_3$), 0.65 (9H, s, $Si(CH_3)_3$), 2.66 (3H, s, CH_3), 2.64 (3H, s, CH_3).
Method B.[3] Trimethylchlorosilane (1 ml) was injected into a suspension of 6,7-dimethylpterin (100 mg) in pyridine (10 ml) which had been previously deaerated with dry nitrogen. The mixture was stirred at room temperature for 30 min. and was then filtered through dry celite to remove precipitated ammonium chloride, the filtration being carried out in a glove bag filled with dry nitrogen. The filtrate was evaporated under reduced pressure in an atmosphere of nitrogen, and the remaining solid material sublimed as described above to give pure (2).

Hydrogenation of 6,7-dimethyl-4-trimethylsiloxy-2-trimethylsilylaminopteridine.
The disilylated pterin (2)(300 mg) was dissolved in dry deaerated benzene (50ml) in a nitrogen filled flask. Prehydrogenated PtO_2 catalyst (10 mg) in dry benzene was added, and the system was then evacuated and filled with hydrogen several times. The reaction mixture was stirred under hydrogen at atmospheric pressure for three hours, but no uptake of hydrogen occurred. A few drops of benzene which had been saturated with water were then added from a pressure equalising dropping funnel at intervals over a period of 48 h. Hydrogen uptake began shortly after the first addition, and after two days, appreciable amounts of solid material had precipitated from solution. The hydrogen was replaced with nitrogen, and 6M hydrochloric acid (20 ml) was then added to the reaction mixture. The catalyst was removed by filtration on a filter stick under nitrogen, and the aqueous acid layer removed and evaporated, affording the hydrochloride of 6,7-dimethyl-5,6,7,8-tetrahydropterin (3) as a pale yellow powder (212 mg; 85%).[4,8,9] It was stored under nitrogen. $\lambda_{max.}$ (0.1M HCl) 220 and 267nm ; δ_H (0.5M DCl) 1.33 (6H, t, J=6.4 Hz, 6-CH_3 and 7-CH_3), 3.9 (2H, m, 6-H and 7-H).

3,6,7-Trimethyl-2-trimethylsilylamino-4(3H)-pteridinone (6).
3,6,7-Trimethyl-4(3H)-pteridinone [17] (300 mg) was suspended in hexamethyldisilazane (20 ml) containing a few crystals of ammonium sulphate, and the mixture refluxed until a clear solution was obtained. After cooling, the resulting white crystals of (6) were collected (260 mg; 63%) on a filter stick under nitrogen, $\lambda_{max.}$ (cyclohexane) 238, 278, 343 and 360(sh) nm ; δ_H ($CDCl_3$) 0.42 (9H, s, $Si(CH_3)_3$), 2.62 (6H, s, 6-Me and 7-Me), 3.57 (3H, s, 3-CH_3) 4.39 (1H, br s, N^2-H).

Hydrogenation of 3,6,7-trimethyl-2-trimethylsilylamino-4(3H)-pteridinone (6).
The monosilylated pteridine (6) (270 mg) was dissolved in dry deaerated benzene

(25 ml) under nitrogen. PtO_2 catalyst (10 mg) was added and the reaction mixture stirred in an atmosphere of hydrogen for 48 h. 6M HCl (20 ml) was then added and the mixture shaken, after which the catalyst was removed by filtration on a filter stick under nitrogen. The aqueous acid layer was removed and evaporated under nitrogen, to give crystals of the hydrochloride of 3,6,7-trimethyl-5,6,7,8-tetrahydropterin (4) (200 mg; 66%), $\lambda_{max.}$ (0.1M HCl) 215 and 256 nm ; δ_H (0.5M DCl) 1.33 (6H, t, J=6.6 Hz, 6-CH_3 and 7-CH_3), 3,39 (3H, s, N-CH_3), 3.9 (2H, m, 6-H and 7-H).

2-Methylamino-6,7-bis(trideuteromethyl)-4(3H)-pteridinone (7).
3,6,7-Trimethyl-4(3H)-pteridinone [17] (500 mg) in a 2M solution of NaOD in D_2O (35 ml) was heated at 100° for 24 h in a stainless steel pressure vessel. After cooling, the yellow precipitate was collected, washed successively with water, ethanol, and ether, and dried in air, to give 410 mg (78%) of compound (7),[17] $\lambda_{max.}$ (0.1M HCl) 218, 250sh and 324 nm ; (0.1M NaOH) 258, 362 nm ; δ_H (0.5M DCl) 3.17 (3H, s, N-Me).

cis-2-Methylamino-6,7-bis(trideuteromethyl)-5,6,7,8-tetrahydro-4(3H)-pteridinone (8).
A yellow solution of 2-methylamino-6,7-bis(trideuteromethyl)-4(3H)-pteridinone (7) (130 mg) in trifluoroacetic acid (6 ml) was added to a prehydrogenated suspension of PtO_2 catalyst in trifluoroacetic acid (4 ml). The mixture was hydrogenated at atmospheric temperature and pressure for 45 min, after which time the yellow colour was discharged. The catalyst was filtered off under nitrogen, methanol (8 ml) containing concentrated hydrochloric acid (2 ml) was added to the filtrate, and the resulting solution was then cooled in ice. Dropwise addition of dry ether to the cold solution, and storage at 0° for 24 h. gave 30 mg (25%) of white crystals of compound (8), which were collected. A second crop (50 mg; 40%) was obtained when the mother liquor was cooled for another 4 days at 0°. $\lambda_{max.}$ (0.1M HCl) 222 and 268 nm ; δ_H (D_2O) 3.15 (3H, s, N-CH_3), 3.9 (2H, br s; in 0.5M DCl, this singlet was resolved into an AB quartet, J=3.3 Hz, 6-H and 7-H).

Desilylation of 6,7-dimethyl-4-trimethylsiloxy-2-trimethylsilylaminopteridine (2) with Rh(DIOP)Cl complex catalyst.
The catalyst was prepared[18] by dissolving dry (-)-DIOP (39.7 mg) in a solution of dry $[Rh(COD)Cl]_2$ (18 mg) in dry deaerated benzene (6 ml) and stirring under nitrogen at room temperature for 15 minutes, during which time the colour changed from pale yellow to orange. Working in a glove bag filled with dry nitrogen, a portion (3 ml) of the catalyst solution was added to a solution of disilylated pteridine (2) (170 mg) in dry deaerated benzene, to give a clear orange colored solution which was stirred under hydrogen at room temperature and pressure. No hydrogen was absorbed, but after 45 min. the solution began to turn cloudy, and after 2 h. appreciable amounts of solid had precipitated from solution. The mixture was stirred for 48 hours, when the solid was collected under nitrogen using a sintered glass filter stick, giving 90 mg (98%) of 6,7-dimethylpterin (1), $\lambda_{max.}$ (0.1M HCl) 215, 252 and 320 nm ; (0.1M NaOH) 250 and 356 nm ; δ_H (0.5M DCl) 2.69 (3H, s, Me) and 2.64 (3H, s, Me). The same result was obtained if the reaction mixture was stirred under nitrogen instead of hydrogen. Neither was any difference made by pre-hydrogenating the catalyst solution by stirring it in an atmosphere of hydrogen for one hour before addition of the pteridine. Control experiments with the disilyl compound dissolved in benzene, but with no rhodium catalyst present, gave no precipitation of solid under the same conditions. Solutions of the rhodium complex prepared as described above were shown to be catalytically active by their ability to catalyse the hydrogenation of α-benzamidocinnamic acid to N-benzoylphenylalanine in 90% yield.

Effect of thiophene on the desilylation of (2) with Rh(DIOP)Cl catalyst.
The catalyst solution was prepared as described above by dissolving (-)-DIOP (39.7 mg) in a benzene solution of $[Rh(COD)Cl]_2$ (18 mg) and stirring under nitrogen for 15 minutes. One drop of thiophene was then added and the solution stirred at room temperature for a further hour. 1 ml of this solution was injected through a septum into a solution of 6,7-dimethyl-4-trimethylsiloxy-2-trimethylsilylaminopteridine (2) (200 mg) in dry benzene under nitrogen. A heavy precipitate of 6,7-dimethylpterin appeared almost immediately, and was collected on a filter stick under nitrogen, and identified by its ^1H n.m.r. spectrum. In a control experiment, a few drops of thiophene were added to a

dry benzene solution of (2) under nitrogen and the resulting solution stirred under nitrogen for 24 hours. No precipitate occurred.

Desilylation of 3,6,7-trimethyl-2-trimethylsilylamino-4(3H)-pteridinone (6) with a Rh(DIOP)-complex catalyst.
The trimethylsilyl pteridine (6) (200 mg) was dissolved in dry deaerated benzene under nitrogen, and to the clear solution was added a dry benzene solution (3 ml) of the Rh(DIOP)-complex catalyst, prepared as described above. The resulting solution was stirred under hydrogen at atmospheric temperature and pressure. A precipitate began to appear within 1 h, and after 3 h the reaction mixture contained appreciable amounts of solid material. After 48 h, the precipitate was collected by filtration under nitrogen on a filter stick, to give 135 mg (92%) of 2-amino-3,6,7-trimethyl-4(3H)-pteridinone, identified by its ^{1}H n.m.r. and u.v. spectra.

Treatment of silylated pteridines (2) and (6) with $[Rh(DIOP)(COD)]^+ClO_4^-$
The catalyst was prepared following a procedure analogous to that described by Schrock and Osborn[19]. A solution of potassium hydroxide (300 mg) in water (1 ml) was added dropwise to a stirred mixture of $[Rh(COD)Cl]_2$ (440 mg), acetylacetone (180 mg), and ether (5 ml), which had been pre-cooled to -80°. The mixture was then allowed to warm up slowly to room temperature over 30 min. when it was filtered to remove any undissolved solids. The filtrate on cooling afforded 250 mg (75%) of Rh(COD)(acetylacetone). This was collected and was dissolved in tetrahydrofuran (3 ml), and to this solution was added a solution of 70% perchloric acid (0.115 g) in tetrahydrofuran (1 ml), followed by (-)-DIOP (399 mg), giving an orange solution. Addition of ether to this precipitated the required catalyst, $[Rh(DIOP)(COD)]^+ClO_4^-$, as an orange solid, which was collected on a filter stick under nitrogen. It was stored under nitrogen at -5°. It was shown to be catalytically active by its ability to catalyse the homogeneous hydrogenation of α-acetamidocinnamic acid to N-acetylphenylalanine in over 90% yield. When a solution of this catalyst in dry deaerated dichloromethane was mixed with a dry solution of either the di- or the mono-silylated pteridine, (2) or (6), and stirred at room temperature under hydrogen, the corresponding de-silylated pteridine was slowly precipitated. No hydrogenated pteridines were formed.

Hydrogenation of 2-amino-4-benzyloxy-6,7-dimethylpteridine (9) in benzene solution over a platinum catalyst
A solution of (9)[15] (80 mg) in dry deaerated benzene containing a PtO_2 catalyst was stirred at room temperature and pressure under hydrogen for 16 h. The catalyst was removed by filtration under nitrogen and the benzene evaporated under vacuum to yield 2-amino-4-benzyloxy-6,7-dimethyl-5,6,7,8-tetrahydropteridine (10) (70 mg; 86%) as a white solid. $\lambda_{max.}$ (0.1M HCl) 232 (sh), 285, 330 nm ; δ_H (0.1M DCl) 1.37 (6H, t, J=6.4 Hz, 6- and 7-CH_3), 3.95 (2H, m, 6- and 7-H), 5.56 (2H, s, O-CH_2), 7.51 (5H, d, Ph).

Hydrogenation of 2-amino-4-benzyloxy-6,7-dimethylpteridine (9) in trifluoroacetic acid solution over a platinum catalyst.
A solution of (9) (50 mg) in trifluoroacetic acid containing a PtO_2 catalyst was stirred at room temperature and pressure under hydrogen for 16 hr. The catalyst was removed by filtration under nitrogen. Methanol (3 ml) containing conc. HCl (250 mg) was added to the filtrate, and the solution was cooled to 0°. An oily layer was obtained which solidified upon addition of ether and evaporating, to give 6,7-dimethyl-5,6,7,8-tetrahydropterin (3) as its hydrochloride (40 mg; 85%)

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