Specific Inhibitors in Vitamin Biosynthesis. Part 8. Syntheses of some Functionalised 7,7-Dialkyl-7,8-dihydropterins

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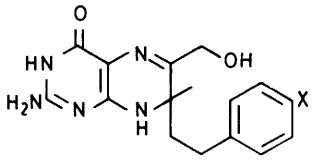
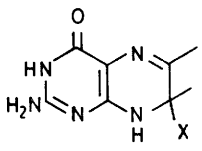
The synthesis of a variety of functionalised blocked 7,8-dihydropteridines is described. The functional groups were chosen to provide compounds with potential for investigating the protein chemistry of enzymes in the pathway leading to dihydrofolate and, in particular, of 6-hydroxymethyl-7,8-dihydropterin pyrophosphokinase. The potential of 7-substituents to provide sites of attachment of inhibitors to columns for affinity chromatography was explored but the extent of the study was curtailed by the restricted applicability of nitrosyl chloride addition to alkenes, a reaction used in the synthesis of pteridine precursors. The syntheses of two compounds, a 6-trichlorophenoxymethyldihydropteridine and of a thiadiazolopteridine, designed to have enhanced transport properties, are also described.

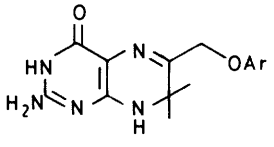
In the previous paper in this series [1] we described several routes to the synthesis of blocked dihydropterins, many of which are inhibitors of 6-hydroxymethyl-7,8-dihydropterin pyrophosphokinase, an enzyme in the pathway leading to 7,8-dihydrofolate. Having obtained a range of lead structures, our attention turned to providing compounds suitable for more detailed investigation of the chemistry of this enzyme. Applications of interest included the further purification of the enzyme by affinity chromatography [2,3] and more extensive probing of the active site by means of affinity labels and other functionalised derivatives of the 7,7-dialkyl-7,8-dihydropterin system. We had also in mind the poor *in vivo* activity of the compounds previously described and wished to prepare a number of derivatives that might behave as pro-drugs, having sufficient permeability to penetrate the bacterial cell together with the latent functionality required for enzyme inhibition. These criteria led to the selection of compounds (**1**)—(**4**) as synthetic targets.



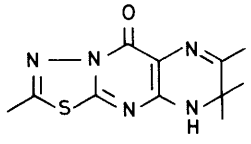
(**1**) X = OR, Cl



(**2a**) X = CH_2OH
(**2b**) X = $[CH_2]_2CO_2H$



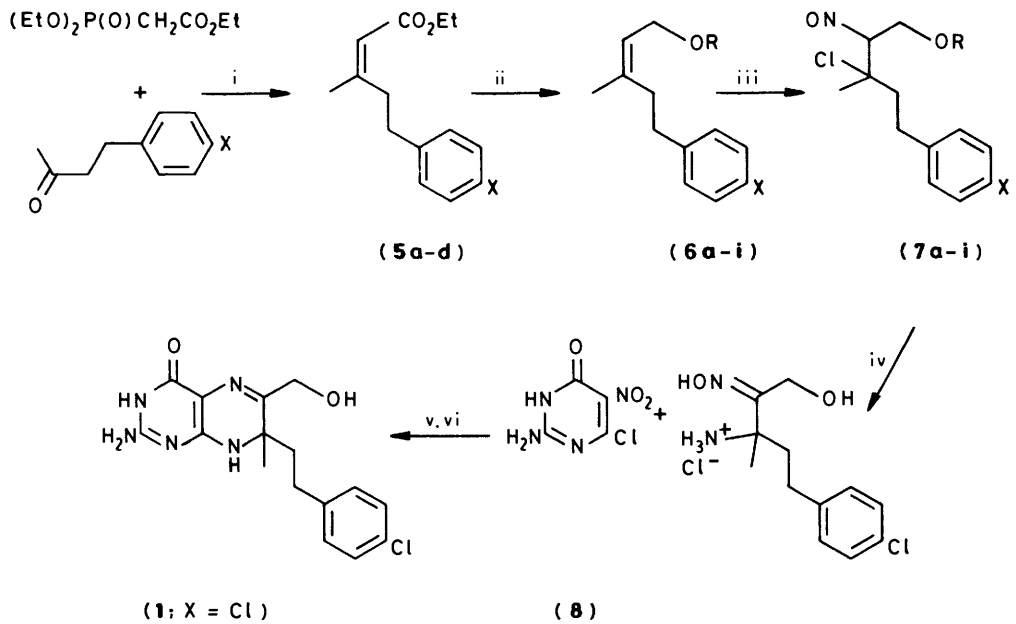
(**3**) Ar = *e.g.*, 2,4,5-trichlorophenyl (TCP)



(**4**)

Synthetic Studies.—The wide variety of substituents selected for study in this investigation, and the difficulties encountered with the routes described previously, led us to avoid attempting a general synthesis. The synthesis of the aralkyl compounds (**1**), however, was approached *via* the nitroso chloride dimers of appropriately substituted alkenes (Scheme 1). As before, the required alkenes were prepared by Wittig reactions of 'triethyl phosphonoacetate' with a suitable ketone followed by reduction of the ester (**5**) with lithium aluminium hydride. However, there were complications with the addition of nitrosyl chloride to give the nitroso chloride dimer adducts (**7**). With the alkenes (**6a** and **b**) the reaction failed to yield the corresponding derivative (**7a** and **b**). Protection of the phenolic alcohol (**6a**) as the diacetate (**6c**) permitted addition to proceed; indeed yields of nitroso chloride dimers were generally better when a protected alcohol [acetate (**6c** and **f**), benzoate (**6d**), methyl ether (**6g** and **h**), or tetrahydropyranyl ether (**6i**)] was used. However, problems were encountered in the ammonolysis. The only compounds in this series to yield the amino ketone readily were the unsubstituted phenethyl [1] and the *p*-chlorophenethyl (**7e**) compounds; intermediates bearing protected hydroxy groups could not be converted into the required amino ketone due either to the stability of the nitroso chloride dimer (**7g** and **h**), the lability of the protecting group (**7i**), or, in the case of the esters, to a rearrangement reaction in which the acyl group migrates (Scheme 2). Unfortunately, we did not succeed in adapting the rearrangement products to produce the required protected amino ketones. The chlorophenethyl compound (**7e**) was converted into the pteridine (**1**; X = Cl) by the standard procedures described in the previous paper.[1]

The next group of modified structures comprised those compounds with polar substituents at C-7. Lack of biological activity for such compounds would provide further evidence for the existence of a non-polar pocket at the enzyme's active site [1] or alternatively, if they were sufficiently potent inhibitors, these compounds would offer a point of attachment for an affinity chromatography ligand to an inert support. Accordingly, the synthesis of the 7-hydroxypropyl and 7-hydroxymethyl compounds was attempted. The former was approached through the nitrosyl chloride route starting from ethyl 4-oxovalerate *via* the enediester (**9**; Scheme 3). The diester (**9**) failed to undergo reduction to the diol with lithium aluminium hydride in ether or tetrahydrofuran (THF) solution, only the non-conjugated ester group being reduced. Red-Al [sodium dihydrobis-(2-methoxyethoxy) aluminate], however, converted the diester into the required diol (**10**) but it was not possible to isolate a crystalline nitroso chloride dimer from this compound. Internal cyclisation of the hydroxypropyl side chain onto the tertiary cation intermediate may have occurred. 7-Functionalised derivatives were, however, obtained from the acetamido ketone (**11**; Scheme 4). This compound was readily available from alanine *via* the Dakin reaction and could be alkylated either with formaldehyde to yield the hydroxymethyl analogue (**12**), or with acrylonitrile

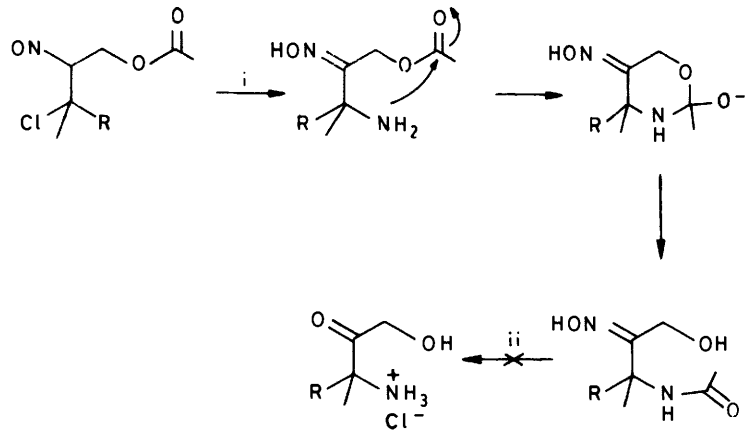


(5a–d) (6a–i) (7a–i)

(1; X = Cl) (8)

(5a—d)	(6a—i)	(7a—i)
a; X = OH	a; X = OH, R = H	a; X = OH, R = H
b; X = OAc	b; X = OMe, R = H	b; X = OMe, R = H
c; X = OMe	c; X = OAc, R = Ac	c; X = OAc, R = Ac
d; X = Cl	d; X = OBz, R = Bz	d; X = OBz, R = Bz
	e; X = Cl, R = H	e; X = Cl, R = H
	f; X = Cl, R = Ac	f; X = Cl, R = Ac
	g; X = Cl, R = Me	g; X = Cl, R = Me
	h; X = H, R = Me	h; X = H, R = Me
	i; X = Cl, R = THP	i; X = Cl, R = THP

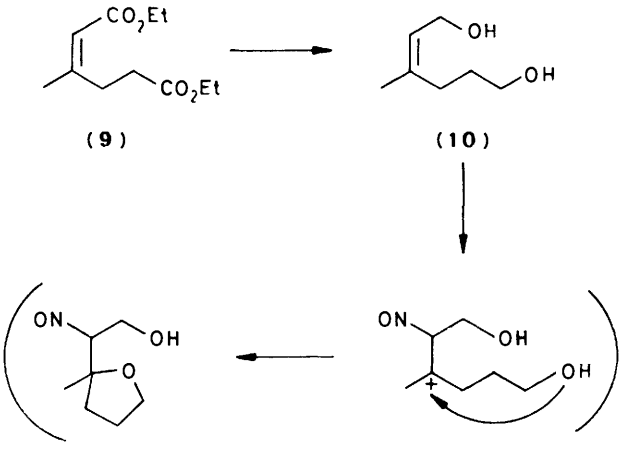
Scheme 1. THP = tetrahydropyran-2-yl. *Reagents:* i, NaH in toluene; ii, $LiAlH_4$; iii, pentyl nitrite–HOAc–HCl or NOCl; iv, MeOH–NH_3; v, Et_3N; vi, aq. $Na_2S_2O_4$.



Scheme 2. *Reagents:* i, NH_3–MeOH; ii, aq. HCl.

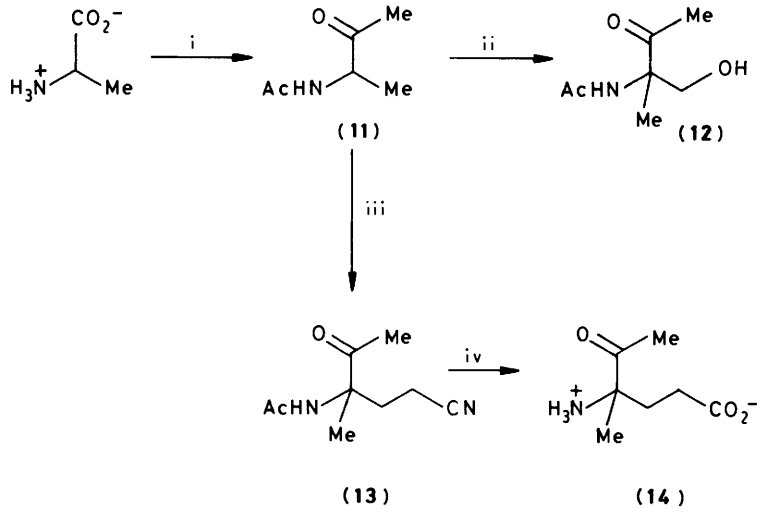
to afford the corresponding cyanoethyl derivative (**13**). Attempts to prepare the hydroxyethyl analogue by addition to ethylene oxide failed. The precursor (**14**) for a potential affinity chromatography ligand was prepared by acid hydrolysis of the nitrile (**13**). Both this acid and the hydroxymethyl compound (**12**) were converted into their semicarbazones prior to coupling with 2-amino-6-chloro-5-nitropyrimidin-4(3*H*)-one (**8**) in the usual way; the reaction failed with the corresponding ketones. Both the amino ketone derivatives synthesized were successfully reductively cyclised to yield the corresponding pteridines (**2a**) and **b**).

The third group of target molecules contained those in which one of the extant polar functional groups was masked by derivatisation. The use of 6-aryloxymethyl ethers (**3**) was intended to promote transport into the target cell and to provide a reactive leaving group for cleavage to the active 6-hydroxymethyl compounds. Such a cleavage could occur remote from the active site to generate a competitive inhibitor,

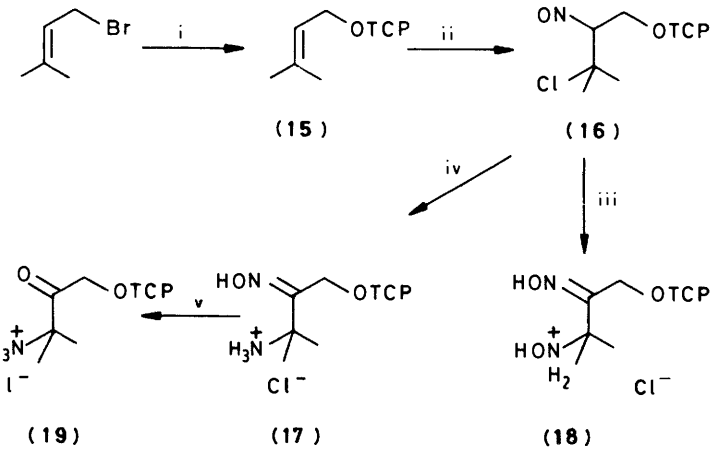


Scheme 3.

led to the required alkene (**15**; Scheme 5) which, on treatment with nitrosyl chloride in chloroform solution, afforded the nitroso chloride dimer (**16**). The use of nitrosyl chloride gas gave much improved yields over pentyl nitrite–hydrochloric acid in this case. The nitroso chloride dimer was converted into the amino oxime (**17**) as usual with methanolic ammonia and an analogous reaction with hydroxylamine led to the hydroxylamino oxime (**18**). Subsequent coupling with the nitrochloropyrimidine (**8**; Scheme 6) led to the pteridine precursor (**20**). The use of the oxime in this case was essential; if coupling was attempted with the ketone (**19**), self condensation occurred to give the pyrazine (**21**). In contrast to the case of the compounds described above, the problems with this synthesis were associated with the final reductive cyclisation. Sodium dithionite in alkaline solution caused hydrolysis of the trichlorophenyl ether, leading to a number of known pteridines (**22**)—(**24**) and a variety of catalytic (Ni, Pd) and dissolving-metal (Al, Zn) reductions failed to give the required product.

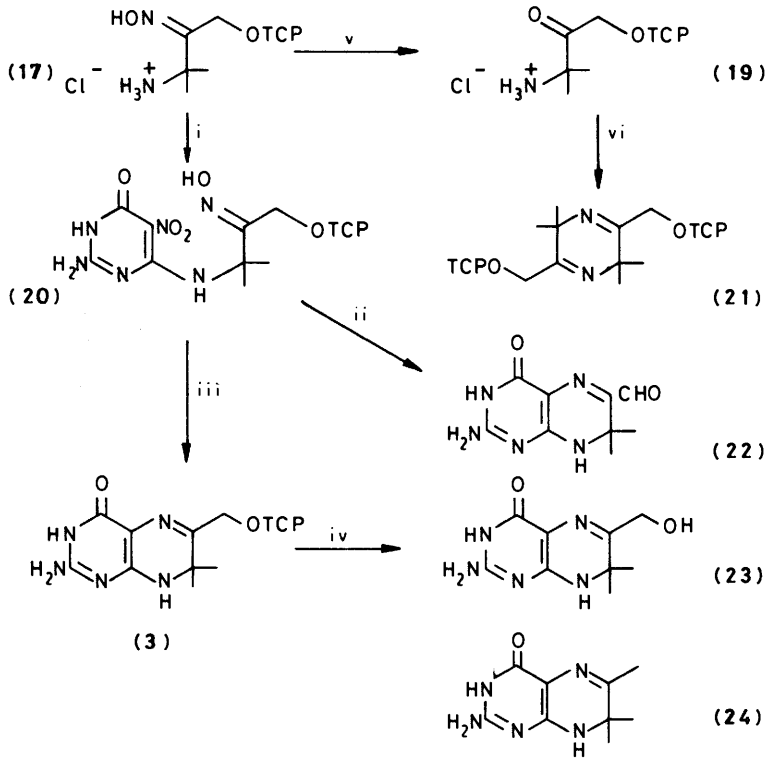


Scheme 4. *Reagents and conditions:* i, Ac_2O–pyridine, 100 °C; ii, aq. HCHO; iii, CH_2=CHCN; iv, aq. HCl.

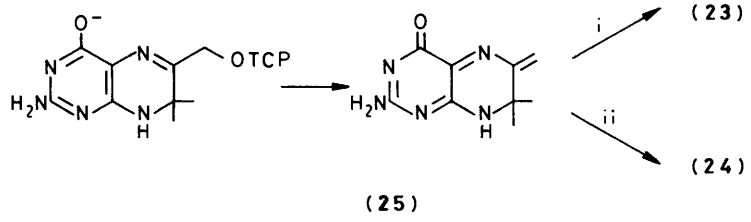


Scheme 5. TCP = 2,4,5-trichlorophenyl. *Reagents:* i, $TCPO^-$; ii, $NOCl$–$CHCl_3$; iii, NH_2OH–MeOH; iv, NH_3–MeOH; v, aq. HCl.

or at the active site in which case irreversible alkylation of the enzyme might take place. The nitroso chloride route was successful in the case of the trichlorophenyl ether (**3**; Ar = TCP). Alkylation of 2,4,5-trichlorophenol with dimethylallyl bromide However, the use of sodium dithionite in neutral aqueous dimethylacetamide (DMA) led to the trichlorophenoxymethylpteridine (**3**) in 33% yield. The high lability of the trichlorophenoxy group is probably due to formation of the



Scheme 6. *Reagents:* i, 2-amino-6-chloro-5-nitropyrimidin-4(3*H*)-one–Et_3N; ii, alkaline aq. $Na_2S_2O_4$; iii, $Na_2S_2O_4$ in CH_3CONMe_2; iv, aq. NaOH; v, H_3O^+; vi, Et_3N–MeOH.

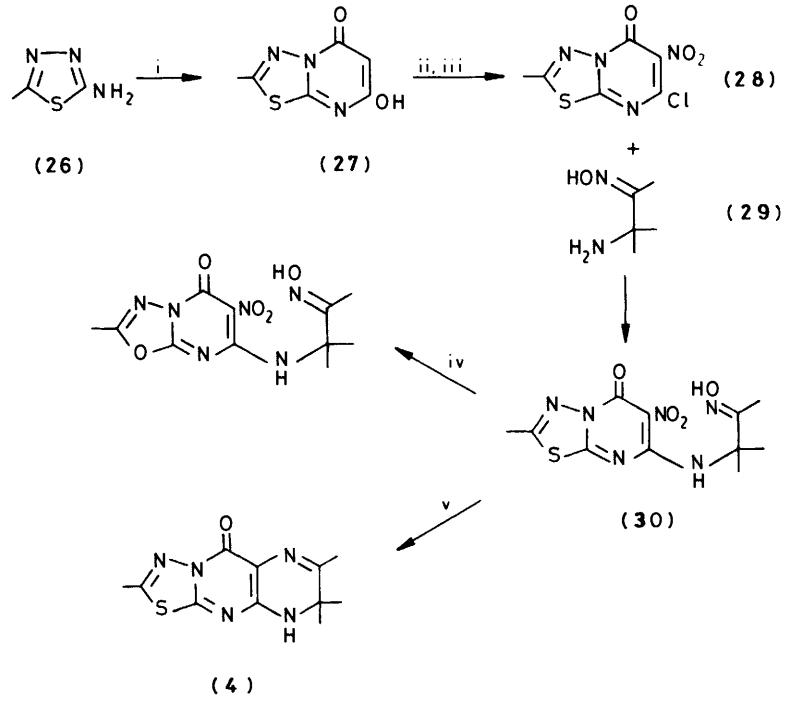


Scheme 7. *Reagents:* i, water; ii, reduction.

anion (Scheme 7) under the conditions of the reduction. In alkaline dithionite, it is likely that the intermediate (**25**), formed by elimination of 2,4,5-trichlorophenoxide, would be reduced, thereby affording the unexpected product, the 6-methylpteridine (**24**). Attempts to prepare the analogous pteridine using pentachlorophenol were abandoned because ammonolysis of the appropriate nitroso chloride dimer caused cleavage of the ether. In view of these problems, one further route was investigated following the alternative strategy for pteridine synthesis *via* pyrazine *N*-oxides developed by Taylor.[4] Although this route is very flexible for pteridines, application to the synthesis of blocked dihydropteridines was not successful. Condensation of the amino ketone (**19**; Scheme 6) with aminocyanoacetamide led not to the anticipated pteridine precursor, but to a self-condensation product (**21**) of the amino ketone. The inability of the reactants to form an *aromatic* pyrazine ring in this case probably promoted the side reaction.

The final compound to be investigated represented an approach to enhancing transport properties of the pteridines by modifying the strongly hydrogen bonding amino-oxo substitution pattern of the pyrimidine ring. The synthesis of a suitable compound (**4**; Scheme 8) was readily achieved by substituting the amino-oxopyrimidine (**28**) for the normal intermediate. Thus the thiadiazole (**26**) was condensed with malonic acid to give the thiadiazolopyrimidine (**27**) which was nitrated with acetyl nitrate and chlorinated with phosphoryl trichloride to give the amino-oxopyrimidine (**28**). This compound was coupled with the amino oxime (**29**) and reductive cyclisation of the intermediate (**30**) with sodium dithionite led to the required pteridine (**4**). However, care was necessary to avoid excessive concentrations of alkali because it was found that the intermediate (**30**) was converted into the oxadiazolo analogue (**31**) when warmed in alkaline solution.

Biological Activity of the Compounds.—The ability of the compounds synthesized above to act as enzyme inhibitors was determined as previously described[1] by measuring the inhibition of the formation of [^{14}C]pteroic acid mediated by the enzyme hydroxymethyldihydropteridine pyrophosphokinase and ATP in the presence of an excess of dihydropteroate synthetase and 4-aminobenzoic acid. The results are shown in the Table and are consistent with the hypothesis put forward in



Scheme 8. *Reagents and conditions:* i, $CH_2(CO_2H)_2$; ii, $AcONO_2$; iii, $POCl_3$; iv, warm aq. NaOH; v, aq. $Na_2S_2O_4$.

Table. Inhibitory properties of some pteridines

Compound	Concentration (μM)	% Inhibition
(1; X = Cl)	4.7	50
(**2a**)	53	5
(**2b**)	120	1
(**3**)	3.2	25
(**4**)	100	9

the previous paper[1] that a hydrophobic pocket exists capable of accommodating the 7-phenethyl-substituted compounds. Thus pteridine (**1**), bearing a non-polar substituent, was active but those compounds with polar substituents in this region, (**2a** and **b**), were very weakly active. Enzymic tests of the remaining two compounds prepared to investigate transport properties of this class of compounds are of lesser significance. The trichlorophenoxy compound (**3**) was an inhibitor but showed no tendency to inactivate the enzyme in a time-dependent manner. The thiadiazolopteridine (**4**), as would be expected, was not an inhibitor. This compound must undergo both hydrolytic opening of the thiadiazole ring and oxidation of the 6-methyl group to become an inhibitor, and *in vivo* experiments are required to test its potential as an antibacterial agent.

Experimental

^{1}H N.m.r. spectra were recorded on Perkin Elmer R10, R14, or R32 spectrometers. Chemical shifts are reported on the δ scale relative to $(CH_3)_4Si$ as internal standard. Spectra marked [a] were obtained at 90 MHz, [b] at 100 MHz, and [c] at 60 MHz.

Ethyl 5-(4-*Hydroxyphenyl*)-3-*methylpent*-2-*enoate* (**5a**).—Ethyl (diethoxyphosphoryl)acetate (23.4 g, 0.1 mol) was added dropwise at 30 °C to a slurry of 80% sodium hydride (7.5 g, 0.25 mol) in dry toluene (500 ml) under a stream of nitrogen. The mixture was stirred for a further 15 min at room temperature. 4-(4-Hydroxyphenyl)butan-2-one (15 g, 0.1 mol) was then added dropwise during 1 h and the resulting solution was stirred at 70 °C for 3 h, when a gelatinous precipitate separated. The mixture was cooled, diluted with water (500 ml), acidified by dropwise addition of conc. hydrochloric acid, and extracted with ether (3 × 200 ml). The combined extracts were washed with water (2 × 200 ml), dried over anhydrous sodium sulphate, and the solvents (ether and toluene) were removed by evaporation. Distillation of the residue gave the α,β-*unsaturated ester* (**5a**) as a liquid (16.8 g, 72%), b.p. 220—230 °C/0.2 Torr (Found: C, 72.1; H, 7.85%; M^+, 234.1243. $C_{14}H_{18}O_3$ requires C, 71.8; H, 7.7%; *M*, 234.1256); $\delta_H(CDCl_3)$[a] 7.1 (1 H, s, OH), 6.7 (4 H, m, ArH), 5.5 (1 H, s, C=CH), 6.0 (2 H, q, CH_2CH_3), 2.8—2.2 (4 H, m, CH_2CH_2Ar), 2.1 (3 H, s, $C=CCH_3$), and 1.2 (3 H, t, CH_2CH_3).

Ethyl 5-(4-*Acetoxyphenyl*)-3-*methylpent*-2-*enoate* (**5b**).—Acetic anhydride (1.5 g, 1.5 × 10^{-2} mol) was added dropwise to a stirred solution of ethyl 5-(4-hydroxyphenyl)-3-methylpent-2-enoate (**5a**) (2.34 g, 1 × 10^{-2} mol) in dry pyridine (5 ml) and the solution was stirred for 16 h. Sodium hydrogen carbonate was then added until effervescence ceased. The product was extracted with ether (2 × 50 ml), and the extracts were washed with water (50 ml), dried over anhydrous sodium sulphate, and the solvents (ether and pyridine) were removed by evaporation. The residue was distilled to give the *ester* (**5b**) as a liquid (2.7 g, 95%), b.p. 240 °C/0.4 Torr (Found: C, 69.9; H, 7.4. $C_{16}H_{20}O_4$ requires C, 69.6; H, 7.25%); δ_H(neat)[a] 6.9 (4 H, m, ArH), 5.6 (1 H, s, C=CH), 4.0 (2 H, q, CH_2CH_3), 2.8—2.2 (4 H, m, CH_2CH_2Ar), 2.1 (3 H, s, $ArOCOCH_3$), 2.0 (3 H, s, $C=CCH_3$), and 1.1 (3 H, t, CH_2CH_3).

5-(4-*Hydroxyphenyl*)-3-*methylpent*-2-*en*-1-*ol* (**6a**).—Lithium aluminium hydride (2.6 g, 7 × 10^{-2} mol) was partially dissolved in dry ether (50 ml) by refluxing for 2 h. A solution of ethyl 5-(4-hydroxyphenyl)-3-methylpent-2-enoate (**5a**) (9 g, 3.8 × 10^{-1} mol) in dry ether (20 ml) was added dropwise to the stirred

mixture, and the resulting suspension was refluxed for 3 h and then stirred at room temperature for 16 h. Saturated aqueous sodium sulphate was added dropwise to the vigorously stirred mixture until a white solid had formed. The precipitate was removed by filtration and washed well with ether. The combined ethereal fractions were washed successively with brine (50 ml) and water (2 × 50 ml) and dried over anhydrous sodium sulphate. The solvent was removed by evaporation and the resulting solid was recrystallised from methylene dichloride to give the *phenolic alcohol* (**6a**) (4.2 g, 55%) as needles, m.p. 62 °C (Found: C, 75.1; H, 8.05. $C_{12}H_{16}O_2$ requires C, 75.0; H, 8.35%); δ_H[$(CD_3)_2SO$][a] 8.9 (1 H, s, ArO*H*), 6.7 (4 H, 2 d, ArH), 5.2 (1 H, t, C*H*CH_2OH), 4.3 (1 H, s, CH_2O*H*), 3.9 (2 H, m, CH_2OH), 2.7—2.2 (4 H, m, CH_2CH_2Ar), and 1.6 (3 H, s, CH_3).

Ethyl 5-(4-*Methoxyphenyl*)-3-*methylpent*-2-*enoate* (**5c**).—Silver oxide (9.2 g, 4 × 10^{-2} mol) and methyl iodide (8.5 g, 6 × 10^{-2} mol) were added to a solution of ethyl 5-(4-hydroxyphenyl)-3-methylpent-2-enoate (**5a**) (4.6 g, 2 × 10^{-2} mol) in dimethylformamide (DMF) (50 ml). The resulting mixture was stirred for 24 h and filtered, and the filtrate was treated with DMF. The combined volumes of DMF were reduced to 10 ml and chloroform (50 ml) was added. The solution was washed with water (2 × 25 ml), dried over anhydrous sodium sulphate, and the solvents were removed by evaporation. The residue was distilled to give the *methoxyphenyl derivative* (**5c**) (4 g, 83%), b.p. 210 °C/0.5 Torr (Found: C, 72.1; H, 8.2%; M^+, 248.1429. $C_{15}H_{20}O_3$ requires C, 72.6; H, 8.05%, *M*, 248.1412); $\delta_H(CDCl_3)$[a] 6.8 (4 H, m, ArH), 5.5 (1 H, s, C=CH), 4.0 (2 H, q, CH_2CH$_3$), 3.6 (3 H, s, OCH_3), 2.8—2.2 (4 H, m, CH_2CH_2Ar), 2.1 (3 H, s, C=CCH_3), and 1.3 (3 H, t, CH_2CH_3).

5-(4-*Methoxyphenyl*)-3-*methylpent*-2-*en*-1-*ol* (**6b**).—Lithium aluminium hydride (0.68 g, 2 × 10^{-2} mol) was partly dissolved in dry ether (20 ml) by refluxing for 2 h. A solution of ethyl 5-(4-methoxyphenyl)-3-methylpent-2-enoate (**5c**) (2.48 g, 1 × 10^{-2} mol) in dry ether (10 ml) was added dropwise to the stirred slurry (temp. < 10 °C). The resulting mixture was stirred at room temperature for 16 h. Saturated aqueous sodium sulphate was added dropwise to the vigorously stirred mixture until a white solid had formed. The precipitate was removed by filtration and washed with ether. The combined ethereal fractions were washed successively with brine (25 ml) and water (25 ml), and dried over anhydrous sodium sulphate. Solvent was removed by evaporation and the residue was distilled to give the *alcohol* (**6b**) as a liquid (1.4 g, 60%), b.p. 220 °C/0.4 Torr (Found: M^+, 206.1295. $C_{13}H_{18}O_2$ requires *M*, 206.1307); $\delta_H(CDCl_3)$[a] 6.8 (4 H, m, ArH), 5.3 (1 H, t, C*H*CH_2OH), 4.0 (2 H, d, CH_2OH), 3.6 (3 H, s, OCH_3), 2.7—2.2 (4 H, m, CH_2CH_2Ar), and 1.6 (3 H, s, CH_3).

5-(4-*Acetoxyphenyl*)-3-*methylpent*-2-*enyl Acetate* (**6c**).—Acetic anhydride (10.8 g, 1.1 × 10^{-1} mol) was added dropwise to a stirred solution of 5-(4-hydroxyphenyl)-3-methylpent-2-en-1-ol (**6a**) (7 g, 6 × 10^{-2} mol) in dry pyridine (70 ml) and the solution was stirred for 16 h. Saturated aqueous sodium hydrogen carbonate was added dropwise until effervescence ceased. The product was extracted with ether (2 × 100 ml), washed with water (100 ml), and dried over anhydrous sodium sulphate, and the solvents (ether and pyridine) were removed by evaporation. The residue was distilled to give the *acetoxy derivative* (**6c**) (7.5 g, 76%), b.p. 210—218 °C/0.1 Torr (Found: C, 69.6; H, 7.35%; *M*, 276.1371. $C_{16}H_{20}O_4$ requires C, 69.6; H, 7.25%; *M*, 276.1361); $\delta_H(CDCl_3)$[a] 6.9 (4 H, 2 d, ArH), 5.2 (1 H, t, C=CH), 4.5 (2 H, d, CH=CH_2), 2.7—2.2 (4 H, m, CH_2CH_2Ar), 2.1 (3 H, s, ArOCOCH_3), 2.9 (3 H, s, CH_2OCOCH_3), and 1.6 (3 H, s, C=CCH_3).

5-(4-*Acetoxyphenyl*)-3-*chloro*-3-*methyl*-2-*nitrosopentyl Acetate Dimer* (**7c**).—A solution of 5-(4-acetoxyphenyl)-3-methylpent-2-enyl acetate (**6c**) (0.28 g, 1 × 10^{-3} mol) and pentyl nitrite (175 mg) in glacial acetic acid (10 ml) was cooled to 5 °C and conc. hydrochloric acid (0.5 ml) was added dropwise, the temperature being kept below 10 °C. The mixture was stirred for 1 h at 5 °C and the resulting precipitate was collected by filtration, washed with cold ether, and air-dried. Recrystallisation from ethyl acetate gave the *nitroso chloride* (**7c**) as the colourless *dimer* (130 mg, 38%), m.p. 117 °C [Found: C, 56.0; H, 6.0; Cl, 10.2; N, 4.4. $(C_{16}H_{20}ClNO_5)_2$ requires C, 56.1; H, 5.85; Cl, 10.4; N, 4.1%]; $\delta_H(CDCl_3)$[a] 7.2—6.8 (4 H, 2 d, ArH), 6.1 (1 H, m, ONCH), 4.6 (2 H, m, CH_2OCOCH_3), 2.8—2.0 (4 H, m, CH_2CH_2Ar), 2.2 (3 H, s, ArOCOCH_3), 1.8 (3 H, s, CH_2OCOCH_3), and 1.6 (3 H, s, CH_3).

5-(4-*Benzoyloxyphenyl*)-3-*methylpent*-2-*enyl Benzoate* (**6d**).—Benzoyl chloride (1.01 g, 7.2 × 10^{-3} mol) was added dropwise to a stirred solution of 5-(4-hydroxyphenyl)-3-methylpent-2-en-1-ol (**6a**) (0.7 g, 3.6 × 10^{-3} mol) in dry pyridine (15 ml). The resulting solution was refluxed for 2 h, poured onto crushed ice (100 ml), and kept until a solid product formed. The solid was collected by filtration, washed with cold water, and dried over phosphorus pentaoxide. Recrystallisation from light petroleum (b.p. 60—80 °C) gave the *benzoyloxy derivative* (**6d**) (0.9 g, 62%), m.p. 36 °C (Found: C, 78.4; H, 6.2%; M^+, 400.1652. $C_{26}H_{24}O_4$ requires C, 78.0; H, 6.0%; *M*, 400.1674), $\delta_H(CDCl_3)$[a] 8.2—7.3 (10 H, m, PhCO), 7.2 (4 H, 2 d, ArH), 5.5 (1 H, t, C*H*CH_2O), 4.8 (2 H, d, CH_2OCO), 2.8—2.2 (4 H, m, CH_2CH_2Ar), and 1.8 (3 H, s, CH_3).

5-(4-*Benzoyloxyphenyl*)-3-*chloro*-3-*methyl*-2-*nitrosopentyl Benzoate* (**7d**) *Dimer*.—A solution of 5-(4-benzoyloxyphenyl)-3-methylpent-2-enyl benzoate (**6d**) (400 mg, 1 × 10^{-3} mol) and pentyl nitrite (200 mg) in glacial acetic acid (10 ml) was cooled to 5 °C and conc. hydrochloric acid (0.5 ml) was added dropwise. The mixture was stirred for 1 h at 5 °C and the resulting precipitate was collected by filtration, washed with cold ether, and air-dried. Recrystallisation from ethyl acetate gave the *nitroso chloride dimer* (**7d**) as colourless needles (200 mg, 43%), m.p. 130 °C [Found: C, 66.9; H, 5.4; N, 3.05. $(C_{26}H_{24}ClNO_5)_2$ requires C, 67.0; H, 5.15; N, 3.0%]; $\delta_H(CDCl_3)$[a] 8.2—7.0 (14 H, m, ArH), 6.4 (1 H, m, ONCH), 4.9 (2 H, m, CH_2OCO), 2.8—2.2 (4 H, m, CH_2CH_2Ar), and 1.6 (3 H, s, CH_3).

Ethyl 5-(4-*Chlorophenyl*)-3-*methylpent*-2-*enoate* (**5d**).—A solution of ethyl (diethoxyphosphoryl)acetate (46 g, 2 × 10^{-1} mol) was added dropwise (temp. > 30 °C) to a slurry of 80% sodium hydride (6 g, 2 × 10^{-1} mol) in dry toluene (200 ml) under a stream of nitrogen. The mixture was stirred for a further 30 min, 4-(4-chlorophenyl)butan-2-one[5] (30 g, 1.6 × 10^{-1} mol) was added dropwise during 1 h, and the resulting solution was stirred at 70 °C for 3 h, when a gelatinous precipitate separated. The mixture was cooled, diluted with water (500 ml), and extracted with ether (2 × 250 ml). The combined extracts were washed with water (250 ml), dried over anhydrous sodium sulphate, and the solvents (ether and toluene) were removed by evaporation. Distillation of the residue gave the α,β-*unsaturated ester* (**5d**) as a liquid (38 g, 83%), b.p. 132 °C/1 Torr (Found: C, 66.5; H, 6.7. $C_{14}H_{17}ClO_2$ requires C, 66.5; H, 6.75%); δ_H(neat)[a] 7.0 (4 H, m, ArH), 5.6 (1 H, s, C=CH), 4.0 (2 H, q, CH_2CH$_3$), 2.8—2.4 (4 H, m, CH_2CH_2Ar), 2.2 (3 H, s, CH_3), and 1.2 (3 H, t, CH_2CH_3).

5-(4-*Chlorophenyl*)-3-*methylpent*-2-*en*-1-*ol* (**6e**).—A stirred solution of ethyl 5-(4-chlorophenyl)-3-methylpent-2-enoate (**5d**) (4.56 g, 2 × 10^{-2} mol) in dry ether (50 ml) was cooled to 0 °C under a stream of nitrogen. Lithium aluminium hydride

(0.5 g, 1.3 × 10^{-2} mol) was added portionwise at 10 °C and the mixture was stirred for 12 h. Saturated aqueous sodium sulphate was then added dropwise to the vigorously stirred mixture until a white solid had formed, and the mixture was then filtered and the residue was washed well with ether. The combined ether washings were washed successively with brine (50 ml) and water (50 ml) and dried over anhydrous sodium sulphate. The solvent was then removed by evaporation and the residue was distilled to give the *alcohol* (**6e**) (2.7 g, 64%), b.p. 205 °C/0.5 Torr (Found: C, 68.8; H, 7.3. $C_{12}H_{15}ClO$ requires C, 68.6; H, 7.15%); δ_H(neat)[a] 6.8 (4 H, m, ArH), 5.3 (1 H, t, C*H*CH_2), 4.4 (1 H, s, CH_2OH), 4.0 (2 H, m, CH_2OH), 2.6—2.1 (4 H, m, CH_2CH_2Ar), and 1.6 (3 H, s, CH_3).

3-*Chloro*-5-(4-*chlorophenyl*)-3-*methyl*-2-*nitrosopentan*-1-*ol Dimer* (**7e**).—(*a*) A solution of 5-(4-chlorophenyl)-3-methylpent-2-en-1-ol (**6e**) (630 mg, 3 × 10^{-3} mol) and pentyl nitrite (600 mg) in glacial acetic acid (10 ml) was cooled to 5 °C and conc. hydrochloric acid (1.5 ml) was added dropwise. The mixture was stirred for 1 h at 5 °C and the resulting precipitate was collected by filtration, washed with cold ether, and air-dried. Recrystallisation from ethyl acetate gave the *nitroso chloride dimer* (**7e**) as colourless needles (100 mg, 12.5%), m.p. 115 °C [Found: C, 52.0; H, 5.25; N, 5.2. $(C_{12}H_{15}Cl_2NO_2)_2$ requires C, 52.1; H, 5.4; N, 4.1%]; δ_H[$(CD_3)_2SO$][a] 8.2 (4 H, m, ArH), 6.0 (1 H, m, CHNO), 4.0 (2 H, s, CH_2OH), 2.8—2.2 (4 H, m, CH_2CH_2Ar), and 1.8 (3 H, s, CH_3).

(*b*) A stirred solution of 5-(4-chlorophenyl)-3-methylpent-2-en-1-ol (**6e**) (1 g, 4.75 × 10^{-3} mol) in dry ether (10 ml) was cooled to −78 °C and a solution of nitrosyl chloride (0.37 g, 5.6 × 10^{-3} mol) in dry ether (10 ml) was added dropwise. The solution was stirred for 15 min at −78 °C, allowed to warm to 0 °C, and stirred for a further 2 h. The resulting precipitate was collected by filtration, washed with cold ether, air-dried, and recrystallised from ethyl acetate to give the nitrosochloride dimer (200 mg, 15%), m.p. 115 °C, identical with that obtained above.

5-(4-*Chlorophenyl*)-3-*methylpent*-2-*enyl Acetate* (**6f**).—Acetic anhydride (1.5 g, 1.5 × 10^{-2} mol) was added dropwise to a stirred solution of 5-(4-chlorophenyl)-3-methylpent-2-en-1-ol (**6e**) (2.1 g, 1 × 10^{-2} mol) in dry pyridine (10 ml) and the solution was stirred for 16 h. Sodium hydrogen carbonate was then added until effervescence ceased. The product was extracted with ether (2 × 25 ml), the extract was washed with water (25 ml) and dried over anhydrous sodium sulphate, and the solvents (ether and pyridine) were removed by evaporation. The residue was distilled to give the *unsaturated ester* (**6f**) as a liquid (2 g, 79%), b.p. 140 °C/0,5 Torr (Found: C, 66.2; H, 6.6%; M^+, 252.0910. $C_{14}H_{17}ClO_2$ requires C, 66.5; H, 6.7%; *M*, 252.0917); δ_H(neat)[a] 7.0 (4 H, m, ArH), 5.2 (1 H, t, C=CH), 4.4 (2 H, d, CH_2OCO), 2.7—2.2 (4 H, m, CH_2CH_2Ar), 1.9 (3 H, s, $COCH_3$), and 1.7 (3 H, s, CH_3).

3-*Chloro*-5-(4-*chlorophenyl*)-3-*methyl*-2-*nitrosopentyl Acetate Dimer* (**7f**).—(*a*) A solution of 5-(4-chlorophenyl)-3-methylpent-2-enyl acetate (**6f**) (0.5 g, 2.5 × 10^{-2} mol) and pentyl nitrite (600 mg) in glacial acetic acid (5 ml) was cooled to 5 °C and conc. hydrochloric acid (1.2 ml) was added dropwise. The mixture was stirred for 30 min at 5 °C and the resulting precipitate was collected by filtration, washed with cold methanol, and air-dried. Recrystallisation from ethyl acetate gave the *nitroso chloride dimer* (**7f**) as colourless needles (300 mg, 55%), m.p. 120 °C [Found: C, 53.0; H, 5.2; N, 4.6. $(C_{14}H_{17}Cl_2NO_3)_2$ requires C, 53.0; H, 5.35; N, 4.4%]; δ_H($CDCl_3$)[a] 7.1 (4 H, 2 d, ArH), 6.2 (1 H, m, CHNO), 4.6 (2 H, m, CH_2O), 2.9—2.2 (4 H, m, CH_2CH_2Ar), 1.9 (3 H, s, $OCOCH_3$), and 1.7 (3 H, s, CH_3).

(*b*) A stirred solution of 5-(4-chlorophenyl)-3-methylpent-2-enyl acetate (**6f**) (0.5 g, 2.5 × 10^{-2} mol) in dry ether (5 ml) was cooled to −78 °C and treated dropwise with a solution of nitrosyl chloride (200 mg, 3.0 × 10^{-3} mol) in dry ether (5 ml). The solution was then stirred for 15 min at −78 °C, allowed to warm to 0 °C, and stirred for a further 2 h. The resulting precipitate was collected by filtration, washed with cold methanol, and dried. Recrystallisation from ethyl acetate gave the nitroso chloride dimer (100 mg, 18%), m.p. 120 °C, identical with that obtained above.

5-(4-*Chlorophenyl*)-3-*methylpent*-2-*enyl Methyl Ether* (**6g**).—Methyl iodide (24 g, 1.7 × 10^{-1} mol) was added dropwise to a solution of 5-(4-chlorophenyl)-3-methylpent-2-en-1-ol (**6e**) (24 g, 1.1 × 10^{-1} mol) and sodium hydride (2.6 g, 1.1 × 10^{-1} mol) in dry toluene (100 ml). The resulting solution was stirred for 16 h, the solvent was removed by evaporation, and water (50 ml) was added. The product was extracted with ether (2 × 100 ml), the combined extracts were washed with water (100 ml) and dried over anhydrous sodium sulphate, and the solvent was removed by evaporation. The residue was distilled to give the methoxypentene (**6g**) as a liquid (18 g, 71%), b.p. 128—130 °C/0.1 Torr; δ_H($CDCl_3$)[a] 7.3—7.0 (4 H, m, ArH), 5.4 (1 H, t, C*H*CH_2OCH_3), 3.9 (2 H, d, CH_2OCH_3), 3.3 (3 H, s, OCH_3), 2.8—2.2 (4 H, m, CH_2CH_2), and 1.7 (3 H, s, CH_3). This compound was further characterised as the nitroso chloride adduct (**7g**).

3-*Methyl*-5-*phenylpent*-2-*enyl Methyl Ether* (**6h**).—Methyl iodide (14 g, 1 × 10^{-1} mol) was added dropwise to a solution of 3-methyl-5-phenylpent-2-en-1-ol[1] (12 g, 6 × 10^{-2} mol) and sodium hydride (2.4 g, 1 × 10^{-1} mol) in dry toluene (100 ml). The resulting solution was stirred for 16 h, the solvent was removed by evaporation, and water (100 ml) was added. The product was extracted with ether (2 × 100 ml), the combined extracts were washed with water (100 ml) and dried over anhydrous sodium sulphate, and the solvent was removed by evaporation. The residue was distilled to give the methoxy derivative (**6h**) as a liquid (9.4 g, 73%), b.p. 110—115 °C/0.1 Torr (Found: M^+, 190.1370. $C_{13}H_{18}O$ requires *M*, 190.1358); δ_H($CDCl_3$)[a] 7.2 (5 H, s, ArH), 5.4 (1 H, t, C*H*CH_2), 3.9 (2 H, d, CH_2OCH_3), 3.2 (3 H, s, OCH_3), 2.8—2.4 (4 H, m, CH_2CH_2), and 1.7 (3 H, s, CH_3). The alkene was further characterised as its nitroso chloride adduct (**7h**).

5-(4-*Chlorophenyl*)-3-*methylpent*-2-*enyl Tetrahydropyran*-2-*yl Ether* (**6i**).—A catalytic quantity of phosphoryl trichloride was added to a stirred solution of 5-(4-chlorophenyl)-3-methylpent-2-en-1-ol (**6e**) (4.2 g, 2 × 10^{-2} mol) and dihydropyran (8.4 g, 1 × 10^{-1} mol) in dry ether (30 ml) and the resulting solution was stirred for 3 h. Water (20 ml) was then added and the product was extracted with ether (3 × 50 ml), and the combined extracts were washed successively with aqueous sodium hydrogen carbonate (25 ml) and water (50 ml) and dried over anhydrous sodium sulphate. The solvent was removed by evaporation and the residue was purified by column chromatography on silica with chloroform as eluant to give the protected alcohol (**6i**) (3.7 g, 72%) as a liquid, δ_H($CDCl_3$)[a] 7.2 (4 H, m, ArH), 5.3 (1 H, m, C=CH), 4.5 (1 H, s, CHO_2), 4.2 (2 H, d, C=CHCH_2O), 3.8 (2 H, m, CH_2OCHO), 2.8—2.2 (4 H, m, CH_2CH_2Ar), 1.9—1.4 (6 H, m, 3 × CH_2), and 1.7 (3 H, s, CH_3). The protected alcohol was further characterised as its nitroso chloride adduct (**7i**).

3-*Chloro*-5-(4-*chlorophenyl*)-3-*methyl*-2-*nitrosopentyl Methyl Ether Dimer* (**7g**).—A solution of 5-(4-chlorophenyl)-3-methylpent-2-enyl methyl ether (**6g**) (1 g, 4.5 × 10^{-3} mol) and pentyl nitrite (1.2 g) in glacial acetic acid (10 ml) was cooled to 5 °C and

conc. hydrochloric acid (2.4 ml) was added dropwise. The mixture was stirred for 1 h at 5 °C and the resulting precipitate was collected by filtration, washed with cold ether, and air-dried. Recrystallisation from ethyl acetate gave the *nitroso chloride dimer* (**7g**) as colourless needles (0.8 g, 61%), m.p. 125 °C [Found: C, 53.4; H, 5.8; Cl, 24.1; N, 5.1. $(C_{13}H_{17}Cl_2NO_2)_2$ requires C, 53.7; H, 5.8; Cl, 24.5; N, 4.8%]; δ_H[$(CD_3)_2SO$]^a 7.2 (4 H, m, ArH), 6.2 (1 H, m, CHNO), 4.0 (2 H, m, CH_2OCH_3), 3.1—2.9 (3 H, 4s, OCH_3), 2.8—2.2 (4 H, m, CH_2CH_2), and 1.7 (3 H, s, CH_3).

3-*Chloro*-3-*methyl*-2-*nitroso*-5-*phenylpentyl Methyl Ether Dimer* (**7h**).—A solution of 3-methyl-5-phenylpent-2-enyl methyl ether (**6h**) (0.5 g, 2.6×10^{-3} mol) and pentyl nitrite (600 mg) in glacial acetic acid (5 ml) was cooled to 5 °C and conc. hydrochloric acid (1.2 ml) was added dropwise. The mixture was stirred for 30 min at 5 °C and the resulting precipitate was collected by filtration, washed with cold methonol, and air-dried. Recrystallisation from ethyl acetate gave the *nitroso derivative dimer* (**7h**) as colourless needles (450 mg, 68%), m.p. 115 °C [Found: C, 61.5; H, 7.3; Cl, 13.7; N, 5.5. $(C_{13}H_{18}ClNO_2)_2$ requires C, 61.4; H, 7.1; Cl, 13.8; N, 5.5%]; $\delta_H(CDCl_3)^a$ 7.2 (5 H, s, ArH), 6.2 (1 H, m, CHNO), 4.0 (2 H, m, CH_2OCH_3), 3.1—2.9 (3 H, s, OCH_3), 2.8—2.2 (4 H, m, CH_2CH_2), and 1.7 (3 H, s, CH_3).

3-*Chloro*-5-(4-*chlorophenyl*)-3-*methyl*-2-*nitrosopentyl Tetrahydropyran*-2-*yl Ether Dimer* (**7i**).—A stirred solution of 5-(4-chlorophenyl)-3-methylpent-2-enyl tetrahydropyran-2-yl ether (**6i**) (0.5 g, 1.8×10^{-3} mol) in dry ether (2 ml) was cooled to −78 °C and a solution of nitrosyl chloride (200 mg, 3×10^{-3} mol) in dry ether (2 ml) was added dropwise. The solution was stirred for a further 3 h. The resulting precipitate was collected by filtration, washed with cold ether, air-dried, and recrystallised from ethyl acetate to give the *nitroso chloride dimer* (**7i**) (100 mg, 15.5%), m.p. 130 °C [Found: C, 56.5; H, 6.6; N, 3.8. $(C_{17}H_{23}Cl_2NO_3)_2$ requires C, 56.6; H, 6.4; N, 3.9%].

2-*Amino*-6-[5-(4-*chlorophenyl*)-1-*hydroxy*-2-*hydroximino*-3-*methylpentan*-3-*ylamino*]-5-*nitropyrimidin*-4(3H)-*one*.—A suspension of 3-chloro-5-(4-chlorophenyl)-3-methyl-2-nitrosopentan-1-ol (**7e**) (2 g, 7.3×10^{-3} mol) in methanolic ammonia (100 ml) was stirred for 3 days. The clear solution obtained was filtered and the filtrate was evaporated to afford a gum which was triturated with dry methanol (10 ml), filtered to remove inorganic material, and the filtrate evaporated to give a foam. Absolute ethanol (75 ml), triethylamine (1.25 g, 1.2×10^{-2} mol), and 2-amino-6-chloro-5-nitropyrimidin-4(3*H*)-one (**8**) (1.75 g, 9×10^{-3} mol) were added. The resulting suspension was refluxed for 8 h, cooled, and filtered. The filtrate was evaporated to leave a gum which upon trituration with ice–water gave a yellow solid. The solid was collected by filtration, washed with water, and reprecipitated from 2M-sodium hydroxide by the addition of 2M-hydrochloric acid to give the title pyrimidine as a pale yellow powder (1.5 g, 52%), m.p. 210 °C (decomp.) (Found: C, 44.2; H, 4.6; N, 21.6. $C_{16}H_{19}ClN_6O_5 \cdot \frac{1}{2}H_2O$ requires C, 45.0; H, 4.9; N, 19.7%); $\lambda_{max.}$ (pH 1) 338; (pH 13) 349 nm; δ_H[$(CD_3)_2SO$]^a 7.0 (4 H, s, ArH), 4.2 (2 H, s, CH_2OH), 2.4—2.0 (4 H, m, CH_2CH_2Ar), and 1.7 (3 H, s, CH_3).

2-*Amino*-7-(4-*chlorophenethyl*)-7,8-*dihydro*-6-*hydroxymethyl*-7-*methylpteridin*-4(3H)-*one* (**1**; X = Cl).—A suspension of 2-amino-6-[5-(4-chlorophenyl-1-hydroxy-2-hydroxyimino-3-methylpentan-3-ylamino]-5-nitropyrimidin-4(3*H*)-one (1 g, 2.4×10^{-3} mol) in 2M-sodium hydroxide (5 ml) was heated to 100 °C and treated portionwise with sodium dithionite. The colour of the solution changed from red to yellow to colourless, further 2M-sodium hydroxide being added when required to ensure an alkaline solution. The resulting suspension was cooled and filtered, and the filtrate was adjusted to pH 8 by the dropwise addition of glacial acetic acid. The resulting solid (0.6 g, 73%) was reprecipitated from 2M-sodium hydroxide with 2M-hydrochloric acid to give the *pteridine hemihydrate* (**1**; X = Cl)·$\frac{1}{2}H_2O$ as a pale green powder, m.p. 155 °C (decomp.) (Found: C, 54.2; H, 5.15; N, 19.4. $C_{16}H_{18}ClN_5O_2 \cdot \frac{1}{2}H_2O$ requires C, 53.9; H, 5.3; N, 19.6%); $\lambda_{max.}$ (pH 1) 357 and 256 (ε 2 105 and 6 842); (pH 13) 330 and 277 nm (ε 2 708 and 3 649 $dm^3\ mol^{-1}\ cm^{-1}$); δ_H[$(CD_3)_2SO$]^a 7.3 (4 H, s, ArH), 4.0 (2 H, s, CH_2OH), 2.8—2.2 (4 H, m, CH_2CH_2Ar), and 1.7 (3 H, s, CH_3).

3-*Methylhex*-2-*ene*-1,6-*diol* (**10**).—A stirred solution of diethyl 3-methylhex-2-enedioate (**9**)[6] (22 g, 0.1 mol) in dry THF (300 ml) under dry nitrogen was treated portionwise with a solution of sodium dihydrobis-(2-methoxyethoxy)aluminate (70% solution in benzene; 90 g, 0.31 mol). The temperature was not allowed to rise above 10 °C. The mixture was stored overnight at room temperature. Saturated aqueous sodium sulphate was added to the mixture until a thick white precipitate had separated. The solid was removed by filtration and washed with THF (2 × 50 ml). The filtrate and washings were combined, washed with brine, dried (anhydrous sodium sulphate), and evaporated to give an oil. The residue was distilled under a short column to give the diol (**10**) (8.3 g, 74%) as a liquid, b.p. 78 °C/0.2 Torr (Found: C, 64.0; H, 11.3. $C_7H_{14}O_2$ requires C, 64.6; H, 10.85%); $\delta_H(CDCl_3)^c$ 5.35 (1 H, t, C=CH), 4.08 (2 H, d, C=CCH_2OH), 3.55 (2 H, t, CH_2CH_2OH), 2.05 (2 H, t, C=CCH_2CH_2), 1.75 (2 H, t, $CH_2CH_2CH_2OH$), and 1.65 (3 H, s, C=CCH_3). This spectrum refers to an inseparable *cis–trans* mixture.

3-*Acetamido*-4-*hydroxy*-3-*methylbutan*-2-*one* (**12**).—3-Acetamidobutan-2-one[7] (**11**) (25.5 g) and paraformaldehyde (7.5 g) were stirred in ethanol (150 ml) in an atmosphere of nitrogen whilst potassium hydroxide (2M in methanol) (10 ml) was added dropwise. The mixture was kept overnight before being neutralised by the addition of conc. hydrochloric acid. The precipitated potassium chloride was removed by filtration (Celite) and the solvent was removed from the filtrate under reduced pressure. The resulting oil solidified to a white crystalline mass (26 g, 86%) which was sufficiently pure for further use. An analytical sample was crystallised from ethanol–toluene to give pure *acetamido ketone* (**12**), m.p. 111—112 °C (Found: C, 52.9; H, 8.35; N, 8.8. $C_7H_{13}NO_3$ requires C, 52.8; H, 8.2; N, 8.8%); $\delta_H(D_2O)^c$ 3.79 (2 H, s, CH_2), 2.17 (3 H, s, $COCH_3$), 2.00 (3 H, s, $NCOCH_3$), and 1.36 (3 H, s, CH_3).

3-*Acetamido*-5-*cyano*-3-*methylpentan*-2-*one* (**13**).—A solution of potassium hydroxide (500 mg) in ethanol (5 ml) was added to a solution of 3-acetamidobutan-2-one (**11**) (18 g) in t-butyl alcohol (9 g). This mixture was stirred, cooled, and treated dropwise with a solution of acrylonitrile (7.5 g) in t-butyl alcohol (11 g), the temperature being maintained below 30 °C. Once the addition was complete the mixture was kept at room temperature for 24 h. The solution was then neutralised (HCl) and filtered (Celite). The filtrate was evaporated under reduced pressure and the residue was crystallised from ethyl acetate to give the *cyano ketone* (**13**) (15 g, 60%) as crystals, m.p. 81.5—82.0 °C (Found: C, 59.4; H, 7.75; N, 15.5. $C_9H_{14}N_2O_2$ requires C, 59.4; H, 7.7; N, 15.4%); $\delta_H(D_2O)^c$ 2.7—2.9 (4 H, m, CH_2CH_2), 2.18 (3 H, s, $COCH_3$), 2.03 (3 H, s, $NCOCH_3$), and 1.33 (3 H, s, CH_3).

3-*Amino*-4-*hydroxy*-3-*methylbutan*-2-*one Hydrochloride*.—3-Acetamido-4-hydroxy-3-methylbutan-2-one (**12**) (10.2 g) was heated under reflux for 2 h in a mixture of water (100 ml) and conc. hydrochloric acid (100 ml). The solvent was removed under reduced pressure to leave a pale red oil which crystallised

from ethanol–ether to give the *title amino ketone hydrochloride* (9.2 g, 93%) as hygroscopic crystals, m.p. 137—140 °C (Found: C, 38.8; H, 7.85; Cl, 23.0; N, 8.8. $C_5H_{12}ClNO_2$ requires C, 39.1; H, 7.8; Cl, 23.1; N, 9.1%); $\nu_{max.}$(KCl) 3 400—2 800, 1 715, 1 600, 1 505, and 1 050 cm^{-1}.

3-*Amino*-4-*hydroxy*-3-*methylbutan*-2-*one Semicarbazone Hydrochloride*.—3-Acetamido-4-hydroxy-3-methylbutan-2-one (**12**) (4 g) was heated under reflux for 2 h in a mixture of water (20 ml) and conc. hydrochloric acid (20 ml). The solvent was removed under reduced pressure and the residue was dissolved in ethanol (14 ml). A solution of semicarbazide hydrochloride (2.7 g) in water (6 ml) was then added and the mixture was kept overnight at 0 °C. The resulting product was removed by filtration and recrystallised from 90% ethanol to give the *title amino ketone semicarbazone hydrochloride* (4.5 g, 85%) as crystals, m.p. 207—209 °C (decomp.) (Found: C, 34.4; H, 7.2; Cl, 16.8; N, 27.1. $C_6H_{15}ClN_4O_2$ requires C, 34.2; H, 7.15; Cl, 16.9; N, 26.6%); $\delta_H(D_2O)^b$ 3.75 (2 H, ABq, *J* 13 Hz, 4-H_2), 1.93 (3 H, s, CH_3C=N), and 1.45 (3 H, s, CH_3C).

2 -*Amino*-6-(1-*hydroxymethyl*-1-*methylacetonylamino*)-5-*nitropyrimidin*-4(3H)-*one Semicarbazone*.—3-Amino-4-hydroxy-3-methylbutan-2-one semicarbazone hydrochloride (5.5 g) and 2-amino-6-chloro-5-nitropyrimidin-4(3*H*)-one (**8**) (4 g) were heated together under reflux for 13 h in absolute ethanol (100 ml) containing dry triethylamine (8 ml). The solvent was removed under reduced pressure and to the resulting gum was added water. The mixture was adjusted to pH 7 with hydrochloric acid and the resulting crude product was removed by filtration. This crude material was treated with hot conc. aqueous ammonia (100 ml) and then cooled to 0 °C. The insoluble ammonium salt was removed by filtration and then dissolved in the minimum volume of boiling water, small quantities of ammonia solution being added to replace ammonia lost to the atmosphere. The solution was filtered, adjusted to pH 7 with hydrochloric acid, and kept overnight. The *title pyrimidine semicarbazone* (4.63 g, 54%) was removed by filtration, m.p. darkens > 260 °C (Found: C, 36.7; H, 4.8; N, 33.7. $C_{10}H_{16}N_8O_5$ requires C, 36.6; H, 4.9; N, 34.1%); $\lambda_{max.}$ (pH 1.5) 337 (ε 16 300); (pH 12.2) 348 nm (ε 19 700 dm^3 mol^{-1} cm^{-1}).

2-*Amino*-7,8-*dihydro*-7-*hydroxymethyl*-6,7-*dimethylpteridin*-4(3H)-*one* (**2a**).—The above pyrimidine semicarbazone (12 g), suspended in boiling water (100 ml), was treated portionwise with sodium dithionite until reduction was complete. The resulting solution was allowed to cool and was then applied to a column of CG-50 ion-exchange resin (H^+ form) (80 cm × 5 cm). The column was washed with degassed water until all the sulphur dioxide and a number of other impurities had been eluted. The eluting solvent was then changed to degassed aqueous formic acid (0.05M). The portion of the eluate which contained the required product (u.v. detection) was collected under nitrogen and the solvent was removed under reduced pressure. The residue was triturated with ethanol and the resulting 7-*hydroxymethylpteridine* (**2a**) (4.4 g, 49%) was filtered off, m.p. > 300 °C (decomp.) (Found: C, 46.9; H, 5.9; N, 29.1. $C_9H_{13}N_5O_2 \cdot C_2H_5OH \cdot \frac{1}{2}H_2O$ requires C, 46.8; H, 6.25; N, 28.8%. Found: M^+, 223.1069. $C_9H_{13}N_5O_2$ requires *M*, 223.1069); $\lambda_{max.}$ (pH 1.4) 362, 271sh, and 254 (ε 6 500, 7 500, and 19 400); (pH 12.4) 323, 281, and 233 nm (ε 7 300, 8 900, and 17 500 dm^3 mol^{-1} cm^{-1}); δ_H(NaOD in D_2O)^c 3.58 (2 H, ABq, *J* 12 Hz, CH_2O), 2.05 (3 H, s, CH_3), and 1.24 (3 H, s, CH_3).

4-*Amino*-4-*methyl*-5-*oxohexanoic Acid* (**14**).—3-Acetamido-5-cyano-3-methylpentan-2-one (**13**) (13 g) was heated under reflux for 2 h in a mixture of water (150 ml) and conc. hydrochloric acid (150 ml). All the volatile material was then removed under reduced pressure and the residue was taken up in a small quantity of water. This solution was applied to a column of Dowex 50-X8 ion-exchange resin (H^+ form) (30 cm × 2.5 cm). The column was washed initially with water and then with aqueous ammonia solution (2M). That portion of the eluate containing the product was collected and the solvent was removed under reduced pressure to give the *amino acid* (**14**) (9.1 g, 80%) as a white powder, m.p. 272—273 °C (Found: C, 52.7; H, 8.0; N, 8.8. $C_7H_{13}NO_3$ requires C, 52.9; H, 8.2; N, 8.8%); $\delta_H(D_2O)^c$ 2.32 (4 H, m, CH_2CH_2), 2.21 (3 H, s, $COCH_3$), and 1.61 (3 H, s, CH_3).

2-*Amino*-6-[1-(2-*carboxyethyl*)-1-*methylacetonylamino*]-5-*nitropyrimidin*-4(3H)-*one*.—A suspension of the above amino acid (**14**) (5 g) and the nitrochloropyrimidine (**8**) (6 g) in a mixture of absolute ethanol (60 ml) and dry triethylamine (60 ml) was stirred at 70 °C for 7 days. Volatile material was removed under reduced pressure and the residue was treated with water (30 ml) and ammonia solution (*d* 0.880; 30 ml). Volatile material was again removed under reduced pressure and the residue was treated with water (20 ml). This mixture was heated to boiling point, filtered whilst hot and, to the boiling filtrate, was added boiling ethanol (250 ml). After this mixture had been allowed to cool to room temperature it was cooled further and stored at 0 °C overnight. The resulting crystalline solid was removed by filtration to give the hemiammonium salt hemihydrate of the *title pyrimidylaminocarboxylic acid* (4.9 g, 50%), m.p. 222—224 °C (decomp.) (Found: C, 38.8; H, 5.35; N, 22.7. $C_{11}H_{15}N_5O_6 \cdot \frac{1}{2}NH_3 \cdot \frac{1}{2}H_2O$ requires C, 38.9; H, 5.45; N, 22.7%); $\lambda_{max.}$ (pH 1.4) 331 (ε 12 800); (pH 13.2) 345 nm (ε 18 650 dm^3 mol^{-1} cm^{-1}); $\delta_H(D_2O)^c$ 2.30 (7 H, m) and 1.57 (3 H, s, $COCH_3$).

4-*Amino*-4-*methyl*-5-*oxohexanoic Acid Oxime*.—The above amino acid (**14**) (1 g), hydroxylamine hydrochloride (0.5 g), and sodium acetate (1 g) were dissolved in water (10 ml) and the mixture was boiled for 5 min. The solution was then concentrated under reduced pressure and kept overnight at 0 °C. The crystalline deposit was removed by filtration and recrystallised from water to give the *title amino acid oxime* (400 mg, 37%) as large prisms, m.p. 188—190 °C (decomp.) (Found: C, 40.4; H, 8.6; N, 13.6. $C_7H_{14}N_2O_3 \cdot 2H_2O$ requires C, 40.0; H, 8.6; N, 13.4%); δ_H(NaOD in D_2O)^c 1.88 (4 H, m, CH_2CH_2), 1.78 (3 H, s, CH_3C=N), and 1.22 (3 H, s, CH_3C).

4-*Amino*-4-*methyl*-5-*oxohexanoic Acid Semicarbazone*.—The amino acid (**14**) (500 mg), semicarbazide hydrochloride (400 mg), and sodium acetate (300 mg) were dissolved in water (3 ml) and the mixture was kept overnight at 0 °C. The crude product was removed by filtration and suspended in water (10 ml). Conc. hydrochloric acid was added dropwise until a clear solution was obtained. This solution was filtered and the filtrate was adjusted to pH 7 with aqueous sodium hydroxide (2M). The mixture was kept overnight and the *title semicarbazone* (400 mg, 58%) was then removed by filtration, m.p. 240 °C (decomp.) (Found: C, 43.5; H, 7.5; N, 25.1. $C_8H_{16}N_4O_3 \cdot H_2O$ requires C, 43.6; H, 7.5; N, 25.4%); δ_H(NaOD in D_2O)^c 1.94 (4 H, m, CH_2CH_2), 1.87 (3 H, s, CH_3C=N, and 1.25 (3 H, s, CH_3C).

2-*Amino*-7-(2-*carboxyethyl*)-7,8-*dihydro*-6,7-*dimethylpteridin*-4(3H)-*one* (**2b**).—The above mentioned pyrimidylaminocarboxylic acid (1.3 g) and sodium hydroxide (600 mg) were dissolved in water (10 ml) and ammonia was removed by evaporation of this solution to dryness under reduced pressure. The residue was dissolved in aqueous sodium hydroxide (2M; 10 ml) and the solution was heated on a steam-bath. To the hot solution was added solid sodium dithionite in portions until reduction was complete. The resulting mixture was cooled and applied to a column of CG-50 ion-exchange resin (H^+ form) (30

cm × 2.5 cm). The column was washed with 20% aqueous methanol and that portion of the eluate which contained the required product (u.v. detection) was collected. The solvent was removed under reduced pressure to give the *7-carboxyethylpteridine* (**2b**) (650 mg, 57%) as a pale yellow powder, m.p. >300 °C (decomp.) (Found: C, 48.6; H, 5.8; N, 24.5. $C_{11}H_{15}N_5O_3 \cdot \frac{1}{2}H_2O$ requires C, 48.2; H, 5.85; N, 25.6%); $\lambda_{max.}$ (pH 1.8) 356, 273sh, and 253 (ε 5 600, 6 500, and 18 000); (pH 12) 325, 279, and 232 nm (ε 6 500, 8 500, and 18 000 dm^3 mol^{-1} cm^{-1}); $\delta_H(D_2O)$[c] 2.34 (3 H, s, CH_3), 2.12 (4 H, m, CH_2CH_2), and 1.60 (3 H, s, CH_3).

3-*Methylbut-2-enyl* 2,4,5-*Trichlorophenyl Ether* (**15**).—A solution of sodium hydroxide (8 g) and 2,4,5-trichlorophenol (39.2 g, 0.2 mol) in a mixture of DMF (162 ml) and water (18 ml) was heated to 65 °C. Dimethylallyl bromide[8] (29.8 g, 0.2 mol) was added dropwise during 1 h and the resulting mixture was heated at 60 °C for 4.5 h. The cooled solution was added to water (800 ml) and the mixture was extracted with ether (4 × 250 ml). The combined extracts were washed successively with 10% aqueous sodium hydroxide (2 × 100 ml) and water (3 × 100 ml), dried (anhydrous sodium sulphate), and evaporated under reduced pressure to give an amber oil (45.5 g). The oil was distilled to give the *title product* (**15**) (29.3 g, 57%) as a colourless liquid, b.p. 126—128 °C/0.8 Torr (Found: C, 49.6; H, 4.5; Cl, 40.3. $C_{11}H_{11}Cl_3O$ requires C, 49.7; H, 4.2; Cl, 40.1%); $\delta_H(CDCl_3)$[c] 7.38 (1 H, s, ArH), 6.95 (1 H, s, ArH), 5.45 (1 H, t, C=CH), 4.53 (2 H, d, CH_2O), 1.79 (3 H, s, CH_3), and 1.74 (3 H, s, CH_3).

3-*Chloro*-3-*methyl*-2-*nitrosobutyl* 2,4,5-*Trichlorophenyl Ether Dimer* (**16**).—(a) *Using pentyl nitrite.* A mixture of 3-methylbut-2-enyl 2,4,5-trichlorophenyl ether (**15**) (13.25 g, 0.05 mol) and pentyl nitrite (7.6 ml, 0.056 mol) in glacial acetic acid (10 ml) was cooled to 0 °C. Conc. hydrochloric acid (5 ml) was added dropwise during 1 h. After a further 1 h at room temperature the mixture was treated with ether (100 ml) and the solid precipitate was collected, washed with dry ether, and dried. The product (4.0 g, 25%) was pure enough for subsequent reactions. A small amount was recrystallised from toluene to give the nitroso chloride dimer (**16**) as pale blue prisms, m.p. 142—143 °C [Found: C, 40.7; H, 3.3; Cl, 41.1; N, 4.1. $(C_{11}H_{11}Cl_4NO_2)_2$ requires C, 39.9; H, 3.4; Cl, 42.9; N, 4.2%].

(b) *Using nitrosyl chloride gas.* A solution of 3-methylbut-2-enyl 2,4,5-trichlorophenyl ether (**15**) (20.0 g) in chloroform (250 ml) was cooled to 2 °C. Nitrosyl chloride was bubbled into the mixture during 2 h. The precipitated nitroso chloride dimer (15.3 g, 62%) was collected, washed with cold chloroform, and dried. The product was identical with that formed in method (a).

3-*Amino*-3-*methyl*-1-(2,4,5-*trichlorophenoxy*)*butan*-2-*one Oxime Hydrochloride* (**17**).—A suspension of 3-chloro-3-methyl-2-nitrosobutyl 2,4,5-trichlorophenyl ether (**16**) (10 g) in a mixture of methanol (100 ml) and toluene (300 ml) was heated under reflux for 2 h. During this period a rapid stream of ammonia was passed through the mechanically stirred mixture. The resulting solution was diluted with methanol (100 ml), cooled, saturated with ammonia, and stored at room temperature overnight. The solution was evaporated to dryness under reduced pressure and a suspension of the residue in water was heated to 90 °C. The mixture was continually adjusted to pH 7 with dil. hydrochloric acid until solution was complete, and was then cooled. The precipitated solid was recrystallised from water to give the *amino oxime hydrochloride* (**17**) *monohydrate* (7.5 g, 73%) as plates, m.p. 208—209 °C (Found: C, 36.3; H, 4.3; Cl, 38.9; N, 7.5. $C_{11}H_{14}Cl_4N_2O_2 \cdot H_2O$ requires C, 36.1; H, 4.4; Cl, 38.8; N, 7.7%); $\delta_H(CD_3OD)$[c] 7.55 (1 H, s, ArH), 7.40 (1 H, s, ArH), 5.08 (2 H, s, CH_2O), and 1.63 (6 H, s, 2 × CH_3).

If the reaction mixture was worked up without acidification, a small quantity (2.8 g) of the free *amino oxime* was recovered. The solid was recrystallised from ethanol as spars, m.p. 116—118 °C (Found: C, 42.2; H, 4.0; Cl, 34.1; N, 8.9. $C_{11}H_{13}Cl_3N_2O_2$ requires C, 42.4, H, 4.2; Cl, 34.1; N, 9.00%); $\delta_H[(CD_3)_2SO]$[c] 7.79 (1 H, s, ArH), 7.59 (1 H, s, ArH), and 4.99 (2 H, s, CH_2O).

3-*Amino*-3-*methyl*-1-(2,4,5-*trichlorophenoxy*)*butan*-2-*one Hydrochloride* (**19**).—A solution of 3-amino-3-methyl-1-(2,4,5-trichlorophenoxy)butan-2-one oxime hydrochloride (**17**) (1 g) in 0.1M-HCl (50 ml) was heated under reflux for 2 h. The cooled solution was evaporated to low volume and the solid was collected by filtration. The product was recrystallised from methanol–acetone to give the *amino ketone hydrochloride* (**19**) (840 mg, 88%) as needles, m.p. 247—248 °C (decomp. >230 °C) (Found: C, 39.7; H, 3.8; Cl, 42.2; N, 4.6. $C_{11}H_{13}Cl_4NO_2$ requires C, 39.7; H, 3.9; Cl, 42.6; N, 4.2%); $\delta_H[(CD_3)_2SO]$[c] 8.78 (3 H, br s, NH), 7.80 (1 H, s, ArH), 7.51 (1 H, s, ArH), 5.55 (2 H, s, CH_2O), and 1.60 (6 H, s, 2 × CH_3).

3-*Hydroxyamino*-3-*methyl*-1-(2,4,5-*trichlorophenoxy*)*butan*-2-*one Oxime Hydrochloride* (**18**).—A mixture of hydroxylamine hydrochloride (0.7 g) and triethylamine (1.5 g) was added to a suspension of 3-chloro-3-methyl-2-nitrosobutyl 2,4,5-trichlorophenyl ether dimer (**16**) (3.5 g) in a mixture of toluene (60 ml) and methanol (60 ml). The mixture was heated under reflux until all the material had dissolved, and was kept at room temperature overnight. The solution was evaporated to leave a solid, which dissolved in methanol and acidified with dil. hydrochloric acid. Re-evaporation of the mixture and recrystallisation of the residue from acetonitrile gave the substituted *hydroxylamine hydrochloride monohydrate* (**18**) (1.25 g, 82%) as beautiful square plates, m.p. 169—170 °C (decomp.) (Found: C, 34.6; H, 4.2; Cl, 37.0; N, 7.4. $C_{11}H_{14}Cl_4N_2O_3 \cdot H_2O$ requires C, 34.6; H, 4.2; Cl, 37.1; N, 7.3%); $\delta_H[(CD_3)_2SO]$[c] 7.80 (1 H, s, ArH), 7.60 (1 H, s, ArH), 5.04 (2 H, s, CH_2O), and 1.57 (6 H, s, 2 × CH_3).

2-*Amino*-6-[3-*hydroxyimino*-2-*methyl*-4-(2,4,5-*trichlorophenoxy*)*butan*-2-*ylamino*]-5-*nitropyrimidin*-4(3H)-*one* (**20**).—A solution of 3-amino-3-methyl-1-(2,4,5-trichlorophenoxy)butan-2-one oxime hydrochloride (**17**) (3.7 g, 0.01 mol), 2-amino-6-chloro-5-nitropyrimidin-4(3*H*)-one (**8**) (1.9 g, 0.01 mol), and anhydrous triethylamine (2.0 g, 0.02 mol) in absolute ethanol (150 ml) was heated under reflux for 6 h. The insoluble material was removed by filtration and the mother liquors were evaporated to leave an amber gum. The gum was triturated with water (100 ml) and the resulting solid was collected. Crystallisation of the residue from ethanol yielded the nitropyrimidine (**20**) (3.4 g, 70%) as pale yellow prisms, m.p. 195 °C (decomp.) (Found: C, 38.3; H, 3.5; Cl, 21.9; N, 17.7. $C_{15}H_{15}Cl_3N_6O_5$ requires C, 38.7; H, 3.2; Cl, 22.9; N, 18.1%); $\delta_H[(CD_3)_2SO]$[c] 8.32 (NH), 2.18, 2.20, 2.40, and 2.45 (2 H, s, ArH *syn*, *anti* mixture), 5.00 (2 H, s, CH_2O), and 1.65 (6 H, s, 2 × CH_3).

2,5-*Dihydro*-2,2,5,5-*tetramethyl*-3,6-*bis*-(2,4,5-*trichlorophenoxymethyl*)*pyrazine* (**21**).—A solution of 3-amino-3-methyl-1-(2,4,5-trichlorophenoxy)butan-2-one hydrochloride (**19**) (165 mg) and triethylamine (50 mg) in methanol (5 ml) was heated under reflux for 3 h. The resulting solid was collected and recrystallised from ethanol to give the *dihydropyrazine* (**21**) (110 mg, 78%) as spars, m.p. 147—149 °C (Found: C, 47.3; H, 3.75; Cl, 38.2; N, 4.9. $C_{22}H_{20}Cl_6N_2O_2$ requires C, 47.4, H, 3.6; Cl, 38.2; N, 5.0%).

Attempted preparations of 2-*Amino*-7,8-*dihydro*-7,7-*dimethyl*-6-(2,4,5-*trichlorophenoxymethyl*)*pteridin*-4(3H)-*one* (**3**).—(*a*) A solution of 2-amino-6-[3-hydroxyimino-2-methyl-4-(2,4,5-tri-

chlorophenoxy)butan-2-ylamino]-5-nitropyrimidin-4(3*H*)-one (**20**) (50 mg) in 0.4M-aqueous sodium hydroxide (12 ml) was treated portionwise at 100 °C with sodium dithionite. The mixture turned from deep yellow to orange and finally to pale yellow. The solution was acidified to pH 4 with glacial acetic acid and was then cooled. The resulting fine crystals (10 mg) were collected and had m.p. 63—65 °C, $\lambda_{max.}$ 310 (pH 14); 290 nm (pH 1). The product was identical with an authentic commercial specimen of 2,4,5-trichlorophenol, m.p. 63—65 °C, $\lambda_{max.}$ 310 (pH 14); 290 nm (pH 1).

(*b*) A suspension of the foregoing nitropyrimidine (**20**) (100 mg) in water (2 ml) was heated to 100 °C, and 2M-aqueous sodium hydroxide (5 drops) was added. Sodium dithionite was added portionwise to the mixture whereupon the solid slowly dissolved and the solution turned through orange to pale yellow. The mixture was cooled and neutralised to pH 7 with glacial acetic acid. The resulting solid was collected by filtration and washed well with ethanol. The product (45 mg) had m.p. > 300 °C. The material was identical (m.p., i.r., n.m.r., u.v.) with an authentic specimen[1] of 2-amino-7,8-dihydro-6,7,7-trimethylpteridin-4(3*H*)-one (**24**).

(*c*) Water (30 ml) was added to a cooled solution of 2-amino-6-[3-hydroxyimino-2-methyl-4-(2,4,5-trichlorophenoxy)butan-2-ylamino]-5-nitropyrimidin-4(3*H*)-one (500 mg) in dimethylacetamide (5 ml). The resulting suspension was centrifuged, the supernatant was discarded, and the solid was re-suspended in water. The precipitate was again collected (centrifuge), the supernatant discarded, and the solid was suspended in water (10 ml). The mixture was heated to 100 °C and treated portionwise with sodium dithionite until a u.v. spectrum of the suspension showed the absence of starting material. The resulting precipitate was collected by centrifugation and washed successively with 1M aqueous sodium hydroxide (10 ml), water (10 ml), cold ethanol (10 ml), and ether (10 ml). The required *pteridine* (**3**) (140 mg, 33%) was purified by reprecipitation from dimethylacetamide (DMA) with water to give a pale yellow powder, m.p. decomp. > 200 °C (Found: C, 45.0; H, 3.7; Cl, 26.5; N, 17.5. $C_{15}H_{14}Cl_3N_5O_2$ requires C, 44.7; H, 3.5; Cl, 26.4; N, 17.4%); $\lambda_{max.}$(EtOH) 235, 281, 300, and 331 nm (ε 29 800, 10 800, 6 500, and 9 730 $dm^3\ mol^{-1}\ cm^{-1}$); δ_H[$(CD_3)_2SO$] 7.60 (1 H, s, ArH), 7.57 (1 H, s, ArH), 6.99 (3 H, s, NH_2 and NH), 4.70 (2 H, s, CH_2O), and 1.29 (6 H, s, 2 × CH_3).

2-Amino-5-methyl-1,3,4-thiadiazole (**26**), *7-hydroxy-2-methyl-1,3,4-thiadiazolo[3,2-a]pyrimidin-5-one* (**27**), *7-hydroxy-2-methyl-6-nitro-1,3,4-thiadiazolo[3,2-a]pyrimidin-5-one, and 7-chloro-2-methyl-6-nitro-1,3,4-thiadiazolo[3,2-a]pyrimidin-5-one.* (**28**).—These were prepared according to procedures supplied by Burroughs Wellcome Co.[9]

7-(3-Hydroxyimino-2-methylbutan-2-ylamino)-2-methyl-6-nitro-1,3,4-thiadiazolo[3,2-a]pyrimidin-5-one (**30**).—A solution of 7-chloro-2-methyl-6-nitro-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one (**28**) (2 g), 3-amino-3-methylbutan-2-one oxime hydrochloride (**29**)·HCl (1.2 g), and triethylamine (1.6 g) in absolute ethanol (50 ml) was heated under reflux for 4 h. The mixture was filtered and the cooled filtrate soon deposited crystals which were collected by filtration and dried. The solid (1.2 g) was recrystallised from ethanol to give the *title nitropyrimidine hemiethanolate* (**30**)·½EtOH as lustrous golden needles, m.p. 206 °C (decomp.) (Found: C, 41.0; H, 4.9; N, 23.9; S, 9.1. $C_{11}H_{14}N_6O_4S{\cdot}\frac{1}{2}C_2H_6O$ requires C, 41.3; H, 4.9; N, 24.1; S, 9.2%); $\lambda_{max.}$(EtOH) 252 and 315 nm (ε 16 990 and 11 890 $dm^3\ mol^{-1}\ cm^{-1}$); δ_H[$(CD_3)_2SO$][c] 2.64 (3 H, s, CH_3CS), 1.77 (3 H, s, CH_3CNOH), and 1.62 (6 H, s, 2 × CH_3); signals for ethanol of crystallisation were observed at δ_H 3.52 (q) and 1.04 (t).

5,6-Dihydro-2,6,6,7-tetramethyl[1,3,4]thiadiazolo[2,3-b]-pteridin-9-one (**4**).—A suspension of the foregoing nitropyrimidine (**30**) (200 mg) in water (5 ml) was heated to 100 °C and 2M-aqueous sodium hydroxide was added until the material had all dissolved. Sodium dithionite was added portionwise to the mixture until the colour had changed from brown to pale yellow. The solution was cooled, adjusted to pH 7 with glacial acetic acid, and the white precipitate was collected by filtration. The product (55 mg, 34%) was purified by reprecipitation from aqueous sodium hydroxide solution with acetic acid to give the *pteridine monohydrate* (**4**)·H_2O as a cream powder, m.p. 290 °C (decomp.) (Found: C, 46.9; H, 5.45; N, 25.2; S, 11.1. $C_{11}H_{13}N_5OS{\cdot}H_2O$ requires C, 46.9; H, 5.3; N, 25.0; S, 11.4%); $\lambda_{max.}$ (pH 1) 267 and 341 (ε 20 440 and 4 740); (pH 14) 282 and 316 nm (ε 12 450 and 6 900 $dm^3\ mol^{-1}\ cm^{-1}$).

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