Specific Inhibitors in Vitamin Biosynthesis. Part 7.[1] Syntheses of Blocked 7,8-Dihydropteridines *via* α-Amino Ketones

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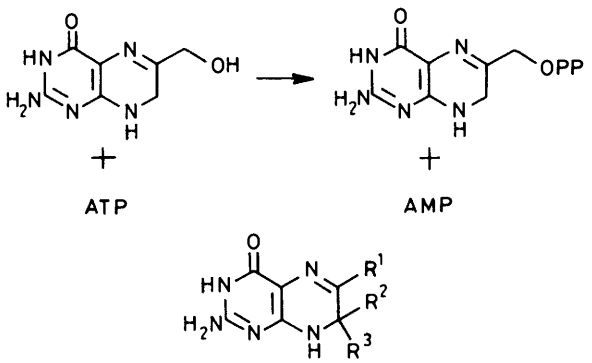
The synthesis of 15 blocked 7,8-dihydropteridines is described in which the pyrazine ring is built from a derivative of an α-amino ketone. Three routes to the amino ketones based upon amino acids, nitrosyl chloride addition to alkenes, and nitro alcohols are discussed. The compounds synthesised are inhibitors of 6-hydroxymethyl-7,8-dihydropterin pyrophosphokinase, an enzyme in the pathway leading to dihydrofolate, and the inhibitory potencies of the compounds are discussed in the light of a hypothetical active site model for the enzyme.

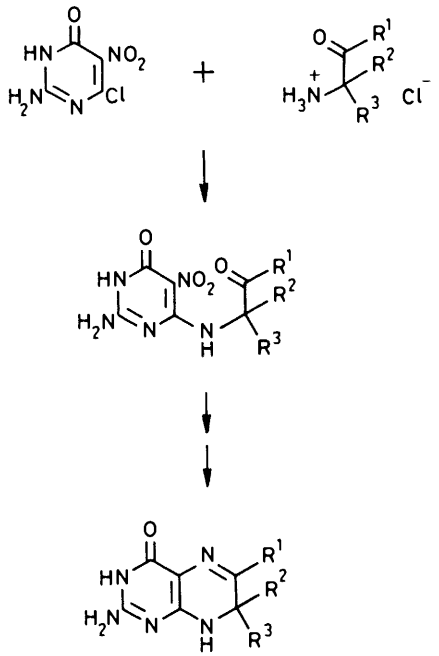
The essence of chemotherapy is the differential effect by which a drug is more toxic to a parasite than to the host; selective toxicity is therefore the key to the design of successful chemotherapeutic agents.[2,3] A particularly favourable opportunity to exploit differences in metabolism between host and parasite is in the biosynthesis of vitamins, pathways for the synthesis of which are absent from the host. Previous papers in this series[4] have applied this design principle to the biosynthesis of riboflavin. Concurrent with these studies, we were also investigating inhibitors of enzymes involved in the biosynthesis of dihydrofolate, and preliminary accounts of this work have appeared[3,5] together with some detailed descriptions in the patent literature.[6] This paper describes synthetic routes to inhibitors of the enzyme 6-hydroxymethyl-7,8-dihydropterin pyrophosphokinase. The inhibitors are all based upon the 7,7-dialkyl-7,8-dihydropterin structure (Scheme 1) and were



Scheme 1. Action of 6-hydroxymethyl-7,8-dihydropterin pyrophosphokinase

designed to be analogues of the natural substrate, and stable to oxidation because of disubstitution at C-7. This general structure permits the elaboration not only of potent inhibitors of this enzyme, but also provides a basis for probing the probable relative arrangement of reacting species at the active site.

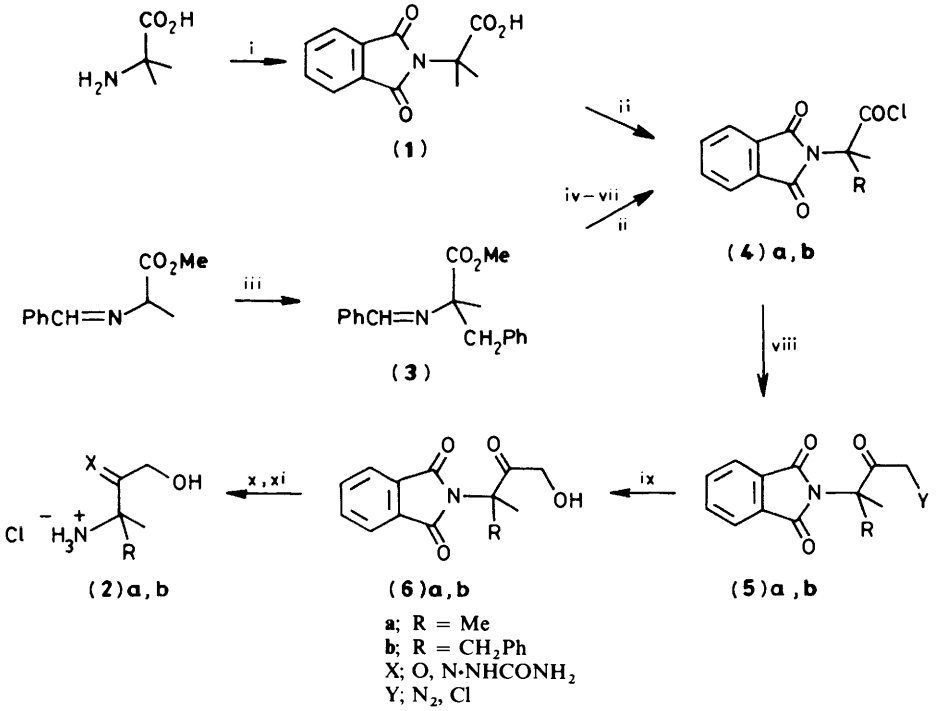
Synthetic Routes to Blocked Dihydropteridines.—The general approach to all the above compounds followed that first described for dihydropteridines by Boon and Jones[7] and used also by Pfleiderer and Zondler[8] in which an appropriately substituted pyrimidine is coupled with an α-amino ketone and



Scheme 2.

the conjugate cyclised (Scheme 2). Since nitrochloropyrimidines are readily available and provide suitably activated substituents for the synthesis, the major problem concerned the synthesis of the α-amino ketone fragment. We have investigated several routes to this type of compound featuring a range of alkyl, aralkyl, and cycloalkyl substituents.

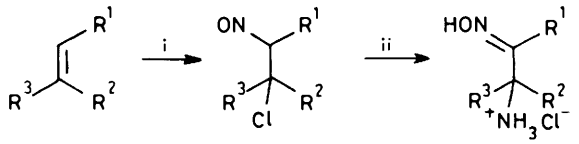
(*a*) Via *amino acid derivatives.* An α-amino acid possesses most of the functionalities required for the construction of the aliphatic portion of the target molecule; starting from alanine, the introduction of a second substituent together with elaboration of the carboxy group to a hydroxymethyl carbonyl system is required (Scheme 3). The first application of this route[6] set out from 2-amino-2-methylpropanoic acid which had been blocked at the amino group using phthalimide protection to give (**1**). Subsequent elaboration of the α-amino ketone was accomplished by treatment of the acid chloride with diazomethane followed by hydrolysis of the diazo ketone and the protecting group. The amino ketone hydrochloride (**2a**) (Scheme 3) was converted into its semicarbazone to avoid self-condensation before coupling to the nitrochloropyrimidine.



Scheme 3. *Reagents:* i, Phthalic anhydride; ii, $SOCl_2$; iii, BuLi, $PhCH_2Br$; iv, 1M HCl; v, $NaHCO_3$; vi, phthalic anhydride; vii, 3M-NaOH; viii, CH_2N_2; ix, aq. H_2SO_4; x, N_2H_4; xi, HCl

Later work has extended this synthesis to provide a route to compounds with different substituents at C-7 of the pteridine. Following Bey and Vevert,[9] benzylidenealanine methyl ester was alkylated with benzyl bromide to give (**3**). It was then necessary to exchange the benzylidene protecting group for the more stable phthalimido group before the molecule could be elaborated to the required amino ketone. Care was also required in choosing the conditions for the formation of the diazo ketone (**5b**; Y = N_2); if diazomethane was added too rapidly to the acid chloride (**4b**) in the absence of triethylamine, the chloro ketone (**5b**; Y = Cl) was formed instead of the required diazo ketone (**5b**; Y = N_2). It proved impossible to hydrolyse the chloro ketone cleanly to the required hydroxy ketone (**6b**) although the latter, on treatment with hydrochloric acid, afforded the chloro ketone. An analogous route[10-12] starting from 3-bromo-3-methylbutan-2-one and sodium azide led to the dihydropteridine (**14h**), a compound which was also prepared *via* the nitro ketone route described below. In principle, this route is generally applicable to the synthesis of precursors of a wide range of potential inhibitors, but is strategically unsatisfactory since the variable alkyl group is necessarily introduced at an early stage.

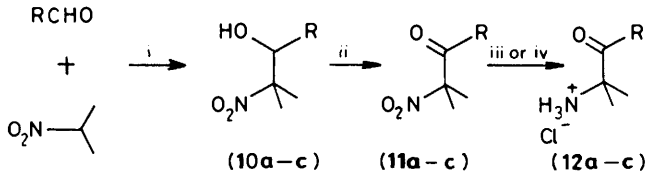
(*b*) *Synthesis from substituted alkenes.* The addition of nitrosyl chloride to suitably substituted alkenes is an attractive approach to the required amino ketones since ammonolysis of the nitrosochloride adduct leads directly to the required amino ketone hydrochloride (Scheme 4). Several of the alkenes used were commercially available (*e.g.* 1-methylcyclopentene and 1-methylcyclohexene) and others were easily accessible *via* the Wittig reaction or through allylic rearrangements. Thus, 2,2-dimethylallyl alcohol was converted into its 3,3-isomer (**7a**) by treatment with boric acid and was then acetylated[13] prior to treatment with nitrosyl chloride. The diethyl (**7c**) and spirocyclohexyl (**7d**) analogues were available from the appropriate ketone and triethyl phosphonoacetate. Subsequent reduction of the ester with lithium aluminium hydride afforded the hydroxymethyl alkenes (**7c**, **d**). This route was preferred to the alternative based upon the Reformatsky reaction[14] because the latter invariably led to mixtures of alkenes on attempted dehydration of the intermediate tertiary alcohols. An analogous sequence of reactions using 4-phenylbutan-2-one as starting material led to a phenylethyl substituted amino ketone (**7e**). The key to the success of this route lay in the properties of the nitrosyl chloride adduct, usually a dimeric nitrosochloride. Unfortunately, the suitability of these derivatives for the purpose at hand proved unpredictable. Although, in general, satisfactory yields were obtainable in the addition reactions provided an insoluble crystalline adduct formed, the more crystalline derivatives sometimes proved inert to ammonolysis. Although the use of nitrosochloride dimers is a short route, once again, the structure-varying step occurs early in the synthesis, and the capriciousness of the reactions makes the more robust but lengthy synthesis *via* amino acids preferable.



	R^1	R^2	R^3
a;	CH_2OH	Me	Me
b;	CH_2OAc	Me	Me
c;	CH_2OH	Et	Et
d;	CH_2OH	$-(CH_2)_5-$	
e;	CH_2OH	Me	CH_2CH_2Ph
f;	$-(CH_2)_3-$		Me
g;	$-(CH_2)_2-$		Me

Scheme 4. *Reagents:* i, NOCl; ii, NH_3 in MeOH

(*c*) *Synthesis via nitroalkanes.* For compounds in which a simple alkyl group is attached to C-6 of the pteridine ring,

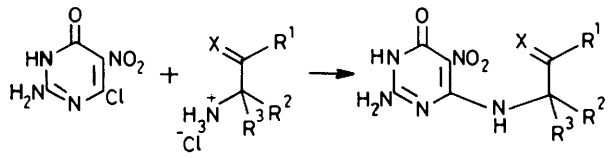


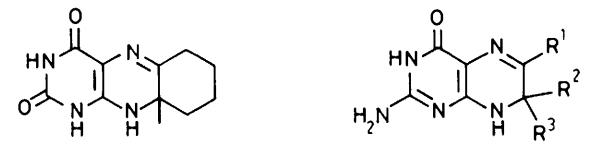
a; R = Me
b; R = Et
c; R = Pr^n

Scheme 5. *Reagents:* i, aq. HO^-; ii, $Na_2Cr_2O_7$, H_2SO_4; iii, Raney Ni; iv, Pd/C, H_2, aq. HCl

synthesis through nitro alcohols is convenient (Scheme 5). 2-Nitropropane was added to straight chain aliphatic aldehydes in a base-catalysed reaction to yield the β-nitro alcohol[15] which was oxidised to the corresponding nitro ketone with acidic dichromate in good yield; the semicarbazone derivatives were also prepared. Hydrogenation of the nitro group was accomplished with either Raney nickel[16] (R = Me), or with palladium–charcoal in the presence of hydrogen chloride (R = Et, Pr^n) and the required amino ketones were obtained in good yield. The utility of this route for the preparation of precursors with elaborate C-6 substituents has not been investigated.

Synthesis of Pteridines.—All the above amino ketones were converted into the required pteridines by the same procedure, differing only in detail to allow for the solubility of the precursors. 2-Amino-6-chloropyrimidin-4(3*H*)-one was nitrated with fuming nitric acid; this reaction required care to obtain good yields, and the most reliable procedure is given in the Experimental section. Nitration both activated the chloro substituent to nucleophilic displacement and provided the remaining nitrogen atom for the pteridine. In the presence of a tertiary base, the amino ketones or their oxime or semicarbazone derivatives were coupled to the pyrimidine (Scheme 6); all were converted into the required blocked dihydropteridines by reduction of the nitro group catalytically or with sodium dithionite, and allowing cyclisation to occur *in situ*. This sequence of operations was very reliable, and only in one case was by-product formation significant. When the cyclohexyl substituted pyrimidine (**13g**) was treated with acid to hydrolyse the oxime prior to cyclisation, the pteridine finally isolated was the lumazine derivative (**15**), analogous to the required 2-aminopteridine, and this structure was confirmed by synthesis. This side reaction, together with the low yields associated with oxime and semicarbazone hydrolysis and the facility with which these less reactive ketone derivatives cyclise, show that attempting such hydrolysis reactions is pointless. Only those pteridines with alcohol or carbonyl substituents at C-6 had significant biological activity. Fortunately, it was unnecessary to develop separate syntheses for the 6,7 cycloalkyl compounds containing these groups because we found that the corresponding saturated compounds underwent remarkably facile oxidation to the corresponding ketones (**14k, l**) under mildly acidic conditions. It was also possible to oxidise the 6-ethyl compound (**14i**) to the 6-acetyl analogue (**14m**). Some studies of mechanistic features of this useful reaction have been undertaken and will be discussed in a subsequent paper describing the reactions of 7,7-dialkyldihydropteridines. Oxidation of 6-





(13a—j), (14a—n)	R^1	R^2	R^3	X
a	CH_2OH	Me	Me	N·$NHCONH_2$
b	CH_2OH	Me	CH_2Ph	N·$NHCONH_2$
c	CH_2OH	Me	CH_2CH_2Ph	N OH
d	CH_2OH	Et	Et	N OH
e	CH_2OH		$-(CH_2)_5-$	N OH
f		$-(CH_2)_3-$	Me	N OH, O
g		$-(CH_2)_4-$	Me	N OH, O
h	Me	Me	Me	N·$NHCONH_2$, O
i	Et	Me	Me	O
j	Pr^n	Me	Me	O
k		$-CO(CH_2)_2-$	Me	
l		$-CO(CH_2)_3-$	Me	
m	COMe	Me	Me	
n	CHO	Me	Me	
o	CHO	Me	CH_2CH_2Ph	

Scheme 6.

Table 1. Inhibitory properties of the pteridines (**14**)

Compd.	Concentration (μM)	% Inhibition
a	2.0	50
b	81	50
c	0.6	50
d	2.0	50
e	100	37
f	54	10
g	31	10
h	75	50
i	38	10
j	110	22
k	50	50
l	50	50
m	5	78
n	17	50

hydroxymethylpteridines to aldehydes (*e.g.* **14a**—**14n**) was also accomplished in good yield using oxygen in the presence of sulphur dioxide.[17]

Biological Activity.—Of the enzymes in the latter part of the pathway leading to dihydrofolate, the pteridines synthesized by the methods above were found to be inhibitors only of hydroxymethyldihydropterin pyrophosphokinase. The inhibitory activity was determined by measuring the inhibition of the production of [^{14}C]pteroic acid in a coupled assay with an excess of the following enzyme, dihydropteroate synthase.[18] Table 1 shows the data obtained expressed as the % inhibition attained (usually 50) at the specified test concentration. It is clear that, whilst almost all compounds showed some inhibition, only those bearing a polar substituent at C-6 were significantly active. The most active compound (**14c**) has in addition a non-polar 7-substituent. The reaction catalysed by the kinase requires ATP and it could be argued that the phenylethyl group in the inhibitor (**14c**) penetrates the pocket into which the adenine ring of ATP usually binds (Figure 1). As will be described in a subsequent paper, pteridines bearing polar substituents at C-7 are very poor inhibitors of the kinase, a result consistent with the existence of a non-polar pocket in this region. Most of the active compounds bear groups that can

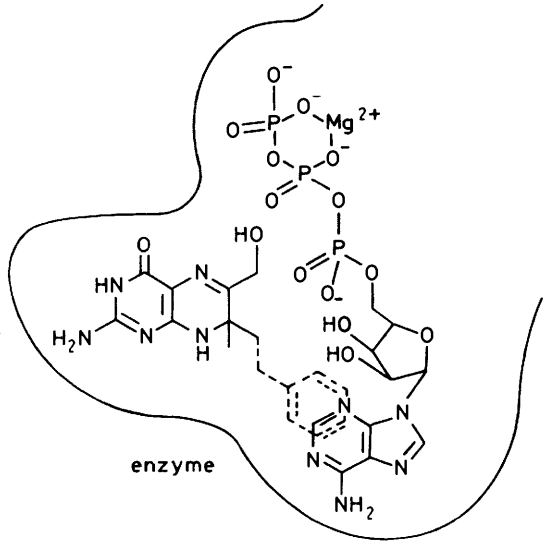


Figure 1.

Table 2. (**14a**): Inhibition of growth of *S. aureus*

Drug (μg ml^{-1})		% Inhibition at 7 h [(**14a**)]/μg ml^{-1}		
Trimethoprim	Sulphamethoxazole	0	5	10
0.002		12	1	39
0.002	0.1	1	99	96
0.002	0.2	14	97	99
0.001	0.1	1	98	98
	0.1	8	89	97

rotate freely about the C-6 substituent bond making a wide range of conformations available. The cycloalkyl ketones (**14k**, **l**) possess polar substituents in defined conformations and retain significant activity. It is therefore possible to suggest that the hydroxyl group of the substrate points away from the C-7 to C-6 bond and approximately parallel to it; the arrangement of reacting groups at the enzyme's active site could be as shown in Figure 1. However, bearing in mind the different orientation of methotrexate and dihydrofolic acid at the active site of dihydrofolate reductase,[19] such deductions can only be made tentatively. In addition to the enzyme inhibition studies, one of the early potent lead compounds (**14a**) was also tested for activity against intact microorganisms. The results with *Staphyllococcus aureus* were disappointing, and it was thought that poor transport of the dihydropteridine into the microorganism's cells could be responsible. (Syntheses of some compounds with the potential to overcome this drawback will be described in a following paper.) However, in combination with sub-effective doses of other inhibitors of folate biosynthesis such as sulphamethoxazole or trimethoprim, a significant synergistic effect was produced by the blocked dihydropteridine (**14a**) (Table 2). A triple combination produced virtually total

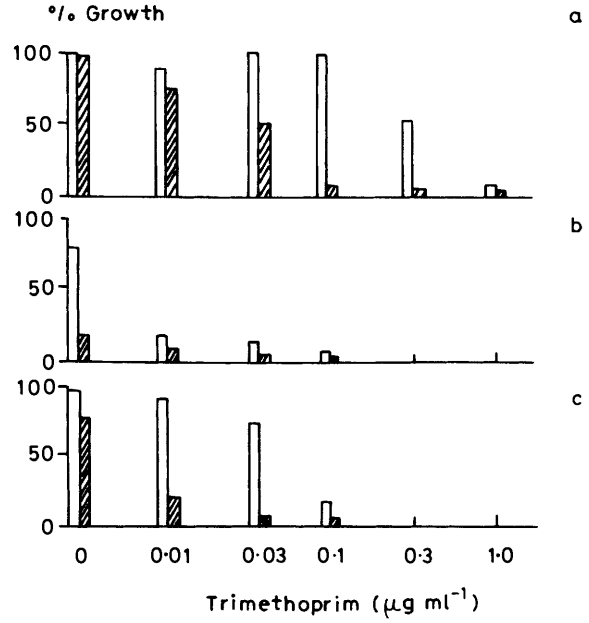


Figure 2. Inhibition of growth of *S. aureus* by the indicated drugs in combination with (**14a**) (10 μg/ml^{-1}): (a) trimethoprim; (b) trimethoprim + sulphamethoxazole (1.0 μg ml^{-1}); (c) trimethoprim + sulphamethoxazole (0.1 μg ml^{-1}). The hatched bars show the % growth with the addition of **14a** and the clear bars the % growth in the presence of trimethoprim and sulphamethoxazole at the concentrations stated in a, b, c

inhibition of growth after 7 hours and corroborative results of a similar experiment are shown in Figure 2. Further details on the unusual synergistic effect, which is apparent with a wide variety of microorganisms, are recorded in the patent literature.[20]

Experimental

^{1}H N.m.r. spectra were recorded on Perkin-Elmer R10 or R32 spectrometers; chemical shifts are reported relative to $SiMe_4$. Spectra labelled [a] were obtained at 90 MHz, [b] at 60 MHz. Light petroleum refers to the fraction boiling in the range 60—80 °C, unless otherwise stated. Ether refers to diethyl ether.

Syntheses related to α-Amino Acids and related Routes

2-Methyl-2-phthalimidopropanoic Acid (**1**).—A mixture of phthalic anhydride (80 g) and 2-aminoisobutyric acid (40 g) was fused at 180—185 °C. The temperature was maintained at 180 °C for 20 min and the melt allowed to cool overnight. It was then dissolved in aqueous sodium hydrogen carbonate (10%, 1 l), filtered, and acidified with concentrated hydrochloric acid. The mixture was cooled and the white crystalline solid was filtered off, washed with water, and dried (60 °C), m.p. 153—154 °C.

2-Methyl-2-phthalimidopropanoyl Chloride (**4a**).—The above acid (75 g) was treated with thionyl chloride (200 ml) under reflux for 1 h. Thionyl chloride was evaporated under reduced pressure, followed by three evaporations with ether to remove residual traces. The residue was recrystallised from light petroleum to give a colourless crystalline solid, m.p. 79 °C.

1-Diazo-3-methyl-3-phthalimidobutan-2-one (**5a**).—An alcohol-free ethereal solution of diazomethane was prepared by adding 'Diazald' (136 g) dissolved in ether (950 ml) dropwise to a flask containing a solution of potassium hydroxide (40.9 g) in water (70 ml), diethylene glycol (240 ml), and ether (70 ml), heated on a water bath at 65—70 °C. The diazomethane formed *in situ* was distilled and collected. To this, a solution of the acid chloride (**4a**) (51.1 g) in ether (700 ml) was added slowly with shaking. The mixture was left overnight at room temperature, after which the ether was evaporated under reduced pressure to give a pale yellow crystalline solid which was used directly in the next reaction.

1-Hydroxy-3-methyl-3-phthalimidobutan-2-one (**6a**).—The above diazo ketone (50 g) was suspended in 0.25M-sulphuric acid (500 ml) and warmed to 80 °C to initiate hydrolysis. After all effervescence had ceased, the mixture was poured into ice–water (1 l) to produce the hydroxymethyl ketone as a crude solid. This was filtered, washed with water (50 ml) and recrystallised from aqueous ethanol (charcoal) to give a pale yellow crystalline solid, m.p. 118 °C.

3-Amino-1-hydroxy-3-methylbutan-2-one Hydrochloride (**2a**).—The above phthalimido ketone (30 g) was treated with 6M-hydrochloric acid (400 ml) under reflux for 2.5 h. The solution was cooled and phthalic acid (19 g), which crystallised out, was removed by filtration. The filtrate was evaporated under reduced pressure and ethanol (50 ml) was added followed by ether (250 ml) to precipitate the amino ketone as hydrochloride. The product was converted into the semicarbazone. Semicarbazide hydrochloride (1 equiv.) was dissolved in the minimum of water and sodium hydrogen carbonate (1 equiv.) was added with stirring until all effervescence had ceased. The amino ketone hydrochloride (1 equiv.) was added portionwise with stirring and the mixture heated on a steam bath for 30 min. The amino ketone hydrochloride semicarbazone (**2a**; X = $NNHCONH_2$) separated as a colourless crystalline mass on cooling, and was filtered off and then washed with alcohol and ether, m.p. 208 °C.

Methyl 2-Benzylideneamino-2-methyl-3-phenylpropanoate (**3**).—This compound was prepared by the method of Bey and Vevert.[9]

Methyl 2-Amino-2-methyl-3-phenylpropanoate.—The benzylidene ester (**3**) (60.4 g, 0.215 mol) was stirred in the presence of 1M-hydrochloric acid (1 l) for 1 h at room temperature and extracted with ether. The aqueous phase was basified with sodium hydrogen carbonate and extracted with ether. The ethereal solution was washed successively with aqueous sodium hydrogen carbonate, water, and brine, and was then dried and concentrated to afford the amine as an oil (39.3 g, 94.4%); a single spot on t.l.c. [(1:1) ethyl acetate–light petroleum] R_F 0.4; $\nu_{max.}(CCl_4)$ 3 365 (NH_2), 1 726 (CO_2Me), and 1 600 cm^{-1} (Ph); $\delta(CDCl_3)$[a] 7.22 (5 H, m, ArH), 3.69 (3 H, s, OMe), 3.12 (1 H, d, *J* 15 Hz, $PhCH_2$), 2.80 (1 H, d, *J* 15 Hz, $PhCH_2$), 1.61 (2 H, s, NH_2), and 1.39 (3 H, s, Me).

Without further purification, the amine was converted into the corresponding half phthalimide.

Methyl 2-(2-Carboxybenzamido)-2-methyl-3-phenylpropanoate.—The above amino ester (2.3 g, 12 mmol) was dissolved in sodium-dried ether (100 ml) and resublimed phthalic anhydride (1.78 g, 12 mmol) was added. The resulting solution was left at room temperature overnight and then extracted with aqueous sodium hydrogen carbonate. The aqueous phase was washed with ether, acidifed with dilute hydrochloric acid, and extracted with chloroform. The resulting organic phase was washed successively with 0.1M-hydrochloric acid, water, and brine, and then dried and concentrated to afford the *amide* as a white powder which recrystallised from chloroform–light petroleum (3.58 g, 92%), m.p. 67—79 °C (Found: *m/z* 341.1264. $C_{19}H_{19}NO_5$ requires *m/z* 341.1263); $\nu_{max.}(CH_2Cl_2)$ 3 380 (NH), 3 400—2 200 (CO_2H), 1 734 (CO_2Me), 1 715 (CO_2H), 1 656 (CONH), and 1 600 cm^{-1} (Ar); $\delta(CDCl_3)$[a] 10.04 (1 H, s, CO_2H), 7.89 (1 H, m, NH), 6.8—7.4 (9 H, m, ArH), 3.72 (3 H, s, OMe), 3.69 (1 H, d, *J* 11 Hz, $PhCH_2$), 3.24 (1 H, d, *J* 11 Hz, $PhCH_2$), and 1.76 (3 H, s, Me).

2-(2-Carboxybenzamido)-2-methyl-3-phenylpropanoic Acid.—The above methyl ester (2.20 g, 6.5 mmol) was dissolved in 1M-sodium hydroxide (3 equiv.) prepared from sodium hydroxide (0.78 g, 19.5 mmol) and water (21.2 ml) and the resulting solution was gently warmed on a steam-bath for 1 h whereupon dilute hydrochloric acid was slowly added until the solution had reached pH 5. The solution was then extracted with ethyl acetate. The organic phase was washed with brine, dried, and concentrated to afford the pure crystalline *dicarboxylic acid* (2.06 g, 98%) m.p. 163—164 °C (Found: C, 66.0; H, 5.3; N, 4.35. $C_{18}H_{17}NO_5$ requires C, 66.05; H, 5.2; N, 4.3%); $\lambda_{max.}$ 218 and 275 nm (ε 26 500 and 3 460 $dm^3\ mol^{-1}\ cm^{-1}$); $\nu_{max.}$ 3 389 (NH), 1 720 (CO_2H), and 1 684 cm^{-1} (CONH); $\delta[(CD_3)_2CO]$[a] 9.85 (2 H, brs, CO_2H), 7.84 (1 H, m, NH), 7.49, (4 H, m, Phth H), 7.24 (5 H, m, Ph), 3.47 (2 H, s, $PhCH_2$), and 1.65 (3 H, s, Me).

2-Methyl-3-phenyl-2-phthalimidopropanoyl Chloride (**4b**).—The above diacid (10.0 g, 30.5 mmol) was refluxed for 1 h with 15 equiv. of triphenyl phosphite-distilled thionyl chloride (33 ml) until all traces of diacid had disappeared. The reaction was most conveniently followed by t.l.c. [1:1 ethyl acetate–light petroleum (b.p. 40—60 °C), 1:1] of a reaction aliquot: R_F acid chloride 0.79, R_F diacid 0.46. The unchanged solvent was removed under reduced pressure to afford a yellow oil which

was dissolved in anhydrous ether and re-evaporated. This process was repeated twice and the resulting yellow oil was dissolved in anhydrous carbon tetrachloride (4 ml) and refrigerated overnight to afford pure, colourless pyramids of sweet-smelling *acid chloride* (9.8 g, 98%), m.p. 74.5—75 °C (Found: C, 65.9; H, 4.3; N, 4.3. $C_{18}H_{14}ClNO_3$ requires C, 65.95; H, 4.3; N, 4.3%); $\lambda_{max.}$ 220 nm (ε 30 700 dm^{-3} mol^{-1} cm^{-1}); $\nu_{max.}(CH_2Cl_2)$ 1 802 (COCl), 1 780, and 1 720 cm^{-1} (Phth); $\delta(CDCl_3)$[a] 7.77 (4 H, Phth-H), 7.11 (5 H, m, Ph), 3.71 (1 H, d, *J* 13 Hz, $PhCH_2$), 3.29 (1 H, d, *J* 13 Hz, $PhCH_2$), and 2.01 (3 H, s, Me).

1-*Diazo*-3-*methyl*-4-*phenyl*-3-*phthalimidobutan*-2-*one* (**5b**; Y = N_2).—An alcohol-free ethereal solution of diazomethane was prepared by adding 'Diazald' (68 g) dissolved in ether (500 ml) dropwise to a flask containing a solution of potassium hydroxide (20.4 g) in water (35 ml), diethylene glycol (120 ml) and ether (40 ml) while warmed on a water-bath in the range 45—55 °C. The diazomethane formed *in situ* was distilled and collected. To this solution was added 1 equiv. (with respect to the acid chloride) of triethylamine (15.4 g, 0.152 mol) and the resulting solution was stirred in an ice-bath in the dark. To this solution was added a solution of the acid chloride (**4b**) (50.0 g, 0.152 mol) in sodium-dried ether (1l) dropwise with stirring over 6 h in the dark. The resulting suspension was stirred overnight at room temperature and then evaporated to dryness under reduced pressure with an aqueous acetic acid trap to destroy the excess of diazomethane. The resulting yellow solid was extracted with ethyl acetate, washed with water and brine, dried, and concentrated to afford yellow needles of the *diazo ketone* (**5b**; Y = N_2) (41.8 g, 91%), m.p. 123—124 °C (Found: C, 68.5; H, 4.5; N, 12.4. $C_{19}H_{15}N_3O_3$ requires C, 68.45; H, 4.5; N, 12.6%). $\lambda_{max.}$ 221, 238, and 276 nm (ε 41 000, 20 300, and 11 500 dm^{-3} mol^{-1} cm^{-1}); $\nu_{max.}(CH_2Cl_2)$ 2 100 (CH_2), 1 771, 1 711 (PhCH), and 1 620 cm^{-1} ($COCHN_2$); $(CDCl_3)$[a] 5.38 (1 H, s, CHN_2), 3.72 (1 H, d, *J* 16 Hz, $PhCH_2$), 3.11 (1 H, d, *J* 16 Hz), and 1.86 (3 H, s, Me).

1-*Chloro*-3-*methyl*-4-*phenyl*-3-*phthalimidobutan*-2-*one* (**5b**; Y = Cl).—(a) An alcohol-free ethereal solution of diazomethane was prepared from 'Diazald' (136 g) as outlined above for the diazo ketone (**5b**; Y = N_2). To this solution at room temperature was slowly added a solution of the acid chloride (**4b**) (50.0 g, 0.152 mol) in anhydrous ether (950 ml) with stirring. The solution was stirred overnight and then filtered to remove the polymer and evaporated to dryness under reduced pressure at room temperature to afford a yellow solid. Recrystallisation from ethyl acetate–light petroleum gave pure diazo ketone (26.5 g, 58%). The remaining mother liquor was column-chromatographed on silica gel (200 g) eluted with light petroleum (b.p. 80—100 °C)–ethyl acetate (85:15 and 65:35) to produce pure *α-chloro ketone* (10.4 g) after recrystallisation from light petroleum–ether, m.p. 112—113 °C (Found: C, 66.7; H, 4.7; N, 4.35. $C_{19}H_{16}ClNO$ requires C, 66.75; H, 5.0; N, 4.35%). $\nu_{max.}$ 220 and 295 nm (ε 22 950 and 1 640 dm^{-3} mol^{-1} cm^{-1}); $\nu_{max.}(CCl_4)$ 1 786, 1 724 (Phth), 1 741 (CO), and 705 cm^{-1} (Ph); $(CDCl_3)$[a] 7.35 (4 H, s, Phth-H), 7.09 (5 H, m, Ph), 4.20 (2 H, ABq, CH_2Cl), 3.71 (1 H, d, *J* 15 Hz, $PhCH_2$), 3.22 (1 H, d, *J* 15 Hz, $PhCH_2$), and 1.90 (3 H, s, Me).

(b) The diazo ketone (**5b**; Y = N_2) (20.0 g, 60 mmol) was warmed on a steam-bath in a solution of 1M-hydrochloric acid (500 ml) and dioxane (150 ml) for 30 min until effervescence had ceased. The solution was basified with sodium hydrogen carbonate and extracted with ether. The organic phase was washed with aqueous sodium hydrogen carbonate and brine, and then dried and concentrated to afford a white powder which was recrystallised from ether–light petroleum to give pure *α-chloro ketone* (18.3 g, 89%), m.p. 112—113 °C, identical in all respects with that produced in (a).

1-*Hydroxy*-3-*methyl*-4-*phenyl*-3-*phthalimidobutan*-2-*one* (**6b**).—The diazo ketone (**5b**; Y = N_2) (20.0 g, 60 mmol) was added to a solution of 0.5M-sulphuric acid (250 ml) and dioxane (150 ml)[21] and the resulting suspension was warmed and stirred on a steam-bath for 45 min until all effervescence had ceased and the α-hydroxy ketone (**6b**) began to precipitate on to the walls of the reaction vessel. The suspension was cooled in an ice-bath, basified with solid sodium hydrogen carbonate, and extracted with chloroform. The organic phase was washed successively with aqueous sodium hydrogen carbonate, water, and brine, and then dried and concentrated to afford the *α-hydroxy ketone* (**6b**) as pale yellow needles (18.6 g, 95%), m.p. 135—136 °C (Found: C, 70.3; H, 5.25; N, 4.35. $C_{19}H_{17}NO_4$ requires C, 70.6; H, 5.3; N, 4.3%); $\nu_{max.}$ 3 515 (OH), 1 771, 1 716, (Phth), and 1 706 cm^{-1} (CO); $\delta(CDCl_3)$[a] 7.71 (4 H, s, Phth-H, 7.09 (5 H, m, Ph), 4.33 (2 H, ABq, CH_2OH), 3.79 (1 H, d, *J* 13.5 Hz, $PhCH_2$), 3.19 (1 H, d, *J* 13.5 Hz, $PhCH_2$), 3.10 (1 H, s, OH), and 1.84 (3 H, s, Me).

3-*Amino*-1-*hydroxy*-3-*methyl*-4-*phenylbutan*-2-*one Hydrochloride* (**2b**; X = O).—The foregoing α-hydroxy ketone (8.64 g, 26.75 mmol), hydrazine hydrate (1.336 g, 1 equiv.), and magnesium ethoxide-dried ethanol (200 ml) were refluxed for 2 h on a steam-bath in a flask equipped with a drying tube. The suspension was then cooled to room temperature and 0.2M-hydrochloric acid (400 ml) was added. The resulting solution was then boiled for 5 min, cooled in an ice-bath, and the precipitated phthaloylhydrazide filtered off. The ethanol was then evaporated off under reduced pressure at 35 °C, the precipitated phthaloylhydrazide was removed by filtration, and the aqueous solution was evaporated to dryness at 35 °C under reduced pressure. The resulting white precipitate was dissolved in water (8 ml), filtered, and crystallised from ethanol–ether to afford pure *amine hydrochloride* (**2b**) (6.02 g, 98%), m.p. 167—168 °C, $\lambda_{max.}$ 216, 253, 258, and 265 nm (ε 2 000, 138, 169, and 150 dm^{-3} mol^{-1} cm^{-1}) $\nu_{max.}$ 1 726 (CO) and 3 600—2 300 cm^{-1} ($RNH_3^+Cl^-$); $\delta[(CD_3)_2SO]$[a] 8.70 (3 H, s, NH_3), 7.30 (5 H, s, Ph), 5.45 (1 H, s, OH), 4.46 (2 H, s, CH_2OH), 3.28 (2 H, s, $PhCH_2$), and 1.58 (3 H, s, Me).

3-*Amino*-1-*hydroxy*-3-*methyl*-4-*phenylbutan*-2-*one Semicarbazone Hydrochloride* (**2b**; X = $NNHCONH_2$).—Semicarbazone hydrochloride (0.486 g, 4.357 mmol) was suspended in anhydrous methanol, (7 ml) and sodium hydrogen carbonate (0.305 g, 1 equiv.) was added. The resulting suspension was stirred at room temperature for 2 h and filtered to remove the sodium chloride. A small amount of water (2 ml) was added and the solution was stirred at room temperature while the above amine hydrochloride (1 g, 4.357 mmol) was added over 1 h. The temperature of the resulting solution was raised to 35 °C over a further 2 h with stirring and the resulting solution was left at 35 °C until no further precipitation of semicarbazone (**2b**) occurred. The suspension was then refrigerated overnight and the crystals filtered off, washed successively with a small amount of ice-cold anhydrous ethanol and ether, and dried to afford pure *semicarbazone hydrochloride* (1.20 g, 97%), m.p. 223—224 °C (Found: C, 50.4; H, 6.6; Cl, 12.35; N, 19.5. $C_{12}H_{19}ClN_4O_2$ requires C, 50.25; H, 6.65; Cl, 12.4; N, 19.55%). $\lambda_{max.}$ 213 and 235 nm (ε 10 600 and 10 600 dm^{-3} mol^{-1} cm^{-1}); $\nu_{max.}$ 3 240 (NH_2), 1 689 (C=N), 1 591 (NCON), and 720 cm^{-1} (ArH); δ(DMSO)[a] 9.38 (1 H, s, OH), 8.32 (3 H, s, NH_3), 7.28 (5 H, s, Ph), 6.59 (2 H, s, NH_2), 6.05 (1 H, s, NH), 4.26 (2 H, s, CH_2OH), 3.19 (2 H, s, $PhCH_2$), and 1.50 (3 H, s, Me).

3-*Azido*-3-*methylbutan*-2-*one*.—3-Bromo-3-methylbutan-2-one[10] (10 g) was dissolved in methanol (250 ml) and a solution of sodium azide (30 g) in water (250 ml) was added. The mixture was refluxed for 1.5 h, cooled, and extracted with light petroleum. The organic layer was dried (Na_2SO_4) and the solvent distilled off through a column (50 cm) until *ca.* 30—35 ml of a greenish liquid was left. Because of its potential instability, this liquid was not further purified: its i.r. spectrum showed peaks at 1 725 cm^{-1} (CO) and 2 125 cm^{-1} (N_3).

3-*Amino*-3-*methylbutan*-2-*one Hydrochloride*.—The above azide was dissolved in ethanol (200 ml) and a concentrated solution of hydrogen chloride in ethanol (20 ml) was added. The solution was stirred under hydrogen with 10% palladium–charcoal (3 g). The catalyst was filtered off and the filtrate was diluted with water and extracted with light petroleum (b.p. 30—40 °C) to remove unchanged azide. The aqueous layer was evaporated under reduced pressure to yield a solid which was recrystallised from ethanol to give the amino ketone hydrochloride as white plates, m.p. 210—211 °C (lit.,[11] 210—211 °C). The azide, recovered from light petroleum, was used again. The overall yield from the bromo ketone was 5.1 g (70%).

3-*Amino*-3-*methylbutan*-2-*one Semicarbazone*.—3-Amino-3-methylbutan-2-one hydrochloride[11] (2.5 g) was dissolved in the minimum quantity of cold ethanol and semicarbazide hydrochloride (2.0 g; 1.1 equiv.) dissolved in the minimum quantity of water was added. The mixture was allowed to stand overnight when the semicarbazone hydrochloride (2.09 g, 80%) separated. Recrystallisation of the latter from water gave the *semicarbazone hydrochloride* as colourless crystals, m.p. 236 °C (Found: C, 36.4; H, 8.2; Cl, 17.5; N, 28.2. $C_6H_{15}ClN_4 \cdot \frac{1}{4}H_2O$ requires C, 36.1; H, 7.75; Cl, 17.6; N, 28.05%). To prepare the free base, a column (2.5 × 15 cm) of Dowex-resin (2-X8, 20—50 U.S. mesh) was washed with 0.1M-sodium hydroxide until the eluate gave a negative test for chloride ion. The column was then washed with carbon dioxide-free distilled water. The semicarbazone hydrochloride (0.86 g) was dissolved in water (10 ml) and the solution was added to the column. The base was eluted with carbon dioxide-free distilled water until the eluate showed a sharp rise in pH. The eluate was evaporated under reduced pressure to yield the *semicarbazone* as a white solid (0.67 g, 95%) m.p. 128—130 °C which gave a negative test for chloride ion (Found: C, 48.8; H, 9.1; N, 35.6. $C_6H_{14}N_4O$ requires C, 45.6; H, 8.9; N, 35.4%); $\delta(D_2O)^b$ 1.93 (3 H, s, Me) and 1.29 (6 H, s, *gem*-dimethyl).

Synthesis via *Nitroso Chlorides*

3,3-Dimethylallyl alcohol (**7a**) and the corresponding acetate (**7b**) were prepared following Young and Webb.[13]

3-*Chloro*-3-*methyl*-2-*nitrosobutanol* (**8a**).—3,3-Dimethylallyl alcohol (5 ml) isopentyl nitrite (7 ml) and glacial acetic acid (10 ml) were cooled in an ice–salt bath. A cooled mixture of concentrated hydrochloric acid (4 ml) and glacial acetic acid (4 ml) was added portionwise with stirring. Towards the end of the addition a white solid precipitated. The reaction mixture was stirred at 0 °C for an additional 15 min, filtered, and the solid washed with a little cold benzene and dried. Recrystallisation from benzene gave the *nitroso chloride dimer* as colourless needles (1.8 g), m.p. 121—122 °C (Found: C, 39.9; H, 6.35; Cl, 23.6; N, 9.1. $C_{10}H_{20}Cl_2N_2O_4$ requires C, 39.6; H, 6.6; Cl, 23.4; N, 9.2%); $\lambda_{max.}$(Nujol) 3 400, 3 500sh, and 3 300sh cm^{-1} (OH); $\delta[(CD_3)_2CO]^b$ 6.20, 6.05 (1 H, 2 d, *J* 5 Hz, C*H*CH_2), 4.20 (2 H, m, CH_2), 3.0 (1 H, br s, OH), and 1.70 and 1.68 (6 H, 2 s, Me).

Similarly prepared was 3-*chloro*-3-*methyl*-2-*nitrosobutyl acetate dimer* (**8b**) (Found: C, 39.8; H, 6.35; Cl, 23.6; N, 9.1. $C_{14}H_{24}Cl_2N_2O_6$ requires C, 39.6; H, 6.6; Cl, 23.45; N, 9.25%); $\lambda_{max.}$(Nujol) 1 730 (acetate) and 1 250 and 1 225 cm^{-1} (acetate); $\delta(CDCl_3)^b$ 6.25 and 6.10 (1 H, 2 d, *J* 5 Hz, CH), 4.70 (2-H, m, CH_2), 2.00 (3 H, s, COMe), and 1.7 (6 H, s, Me).

3-*Amino*-2-*hydroxyimino*-3-*methylbutanol Hydrochloride* (**9a**).—3-Chloro-3-methyl-2-nitrosobutanol (8 g) was dissolved in a solution of methanol (100 ml) saturated with ammonia at 0 °C. The mixture was allowed to stand at 0 °C overnight, and then at room temperature for 5 h; it was then refluxed for 12 h under an atmosphere of ammonia gas. The volatile material was removed at 40 °C and the dark brown residual oil extracted with hot benzene (4 × 25 ml). The benzene-insoluble material was extracted with hot butan-2-ol (3 × 10 ml) giving an insoluble component (identified as ammonium chloride) and a soluble component. The soluble fractions were combined, cooled, and the precipitated solid collected (1.3 g). Concentration of the mother liquors gave a further fraction (2.0 g). These combined crops were triturated with hot acetone, filtered, and recrystallised from butan-2-ol to give the *oxime* as off-white needles (2.5 g), m.p. 172—174 °C (Found: C, 34.8; H, 7.5; Cl, 21.3; N, 16.8. $C_5H_{13}ClN_2O_2$ requires C, 35.5; H, 7.7; Cl, 21.05; N, 16.6%). $\lambda_{max.}$(Nujol) 3 260, 3 320 (OH), 2 600—3 200 (NH_3), 1 600 (CN), and 1 380 [$(Me)_2C$] cm^{-1}; $\delta[(CD_3)_2SO]^b$ 7.5 (2 H, OH), 4.26 (2 H, s, CH_2), and 1.4 (6 H, s, Me).

Ethyl Cyclohexylideneacetate[22].—Sodium-dried benzene (200 ml) was added to sodium hydride (16 g, 0.667 mol) in a flask which was flushed with oxygen-free, dry nitrogen. To this mixture was added, over 1 h, triethyl phosphonoacetate (163.3 g, 10% excess) the temperature being kept at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and then treated with cyclohexanone (65.4 g, 0.667 mol) at the same temperature. After the addition of the cyclohexanone was complete (*ca.* 40 min) the mixture was stirred at room temperature for 3 h; stirring became difficult after this time owing to a gummy precipitate of sodium diethyl phosphate. The mixture was then heated at 60—65 °C for 15 min during which time it was stirred without difficulty. The mixture was cooled to 15 °C when the benzene solution was decanted and the solid washed with benzene. The combined mother liquor and washings were evaporated to give a pale yellow oil which on distillation gave the *title compound* (62 g, 55%) as a colourless oil, b.p. 86—88 °C/2 Torr (Found: C, 71.6; H, 9.6. $C_{10}H_{16}O_2$ requires C, 71.4, H, 9.5%). G.l.c. on 25% methyl silicone gum at 180 °C showed the presence of a single product with R_t 6.6 min; $\lambda_{max.}$(liquid film) 1 710 (CO), 1 645 (C=C), and 865 (C=CH) cm^{-1}; $\delta(CDCl_3)^b$ 5.62 (1 H, s, C=CH), 4.15 (2 H, q, *J* 7 Hz, CO_2CH_2Me), 2.83 (2 H, m, CH_2C=), 2.20 (2 H, m, CH_2C=), 1.63 (6 H, br s, CH_2), and 1.28 (3 H, t, *J* 7 Hz, CH_2Me).

2-*Cyclohexylidene*-*ethanol*[23] (**7d**).—A 70% solution (in benzene) of sodium dihydrobisethoxymethoxyaluminate (100 g, 0.35 mol) was added portionwise to ethyl cyclohexylideneacetate (58.8 g, 0.35 mol) in dry ether (300 ml) at 0 °C. The reaction mixture was stirred for 6 h at room temperature and the excess reducing agent was then destroyed by the addition of water. The solid sodium aluminate was filtered off and the filtrate extracted with ethyl acetate (4 × 50 ml). The combined extracts were washed with brine, dried (Na_2SO_4), and the solvent evaporated under reduced pressure. A pale yellow oil was obtained which on distillation gave 2-cyclohexylideneethanol (31 g, 70%) as a colourless oil, b.p. 80 °C/2 Torr (Found: C, 76.2; H, 11.2. $C_8H_{14}O$ requires C, 76.2; H, 11.1%). G.l.c. on 25% methyl silicone gum at 130 °C showed the presence of a single product with R_t 11.9 min; $\lambda_{max.}$(liquid film) 3 200—3 500 (OH) and 1 670 (C=C) cm^{-1}; $\delta(CDCl_3)^b$ 5.38 (1 H, t, *J* 7 Hz,

CHCH$_2$OH), 4.15 (2 H, d, *J* 7 Hz, CHCH$_2$OH), 2.16 (4 H, m, CH$_2$C=), 1.75 (1 H, s, CH$_2$OH), and 1.56 (6 H, br s, 3 × CH$_2$).

2-(1-*Chlorocyclohexyl*)-2-*nitrosoethanol* (**8d**).—2-Pentyl nitrite (21.5 g, 0.18 mol) was added to 2-cyclohexylidene-ethanol (23 g, 0.18 mol) dissolved in glacial acetic acid (76 ml) and the mixture was cooled in an ice–salt bath. The cooled solution was treated dropwise with cold concentrated hydrochloric acid (23 ml) with stirring. After the addition of the acid was complete the reaction mixture was stirred at the same temperature for 30 min, followed by further cooling in an acetone–solid CO_2 bath for 10 min. The buff-coloured solid was filtered off, washed with cold methanol and recrystallised from acetone to give the *nitroso chloride dimer* (15 g, 43%) as colourless needles, m.p. 130 °C (Found: C, 50.3; H, 7.2; Cl, 18.25; N, 7.2. $C_{16}H_{28}Cl_2N_2O_4$ requires C, 50.1; H, 7.3; Cl, 18.5; N, 7.3%). $\lambda_{max.}$(KCl) 3 460 (OH) and 680 cm^{-1} (CCl); δ[(CD$_3$)$_2$SO][b] 6.8 (1 H, dd, *J* 4 Hz, CHCH$_2$OH), 4.26 (1 H, s, CH$_2$OH), 4.08 (2 H, m, CH$_2$OH), 2.8 (2 H, m, CH$_2$CCl), 1.78 (2 H, m, CH$_2$CCl), and 1.58 (6 H, m, 3 × CH$_2$).

2-(1-*Aminocyclohexyl*)-2-*oxoethanol Oxime Hydrochloride* (**9d**).—A solution of methanol saturated with ammonia was added to the nitrosoethanol (**8d**) (14.5 g, 0.075 mol) in a tightly secured stoppered flask and the mixture was stirred for 3 days at room temperature. The reaction mixture was then refluxed for 1.5 h in an atmosphere of ammonia, cooled and filtered. The solvent was removed and the residual yellow oil washed with hot benzene and decanted. The solid was recrystallised from ethanol to give the *oxime hydrochloride* (7.8 g, 50%) as colourless crystals, m.p. 197 °C (Found: C, 46.0; H, 8.1; Cl, 17.1; N, 13.6. $C_8H_{17}ClN_2O_2$ requires C, 46.0; H, 8.15; Cl, 17.0; N, 13.4%); $\lambda_{max.}$(KCl) 3 300—3 500 (OH), 3 100 (NH$_3$), and 1 600 cm^{-1} (CN); δ[(CD$_3$)$_2$SO][b] 8.45 (1 H, s, NOH), 7.7 (3 H, br s, NH$_3$), 4.42 (2 H, s, CH$_2$OH), 3.35 (1 H, s, CH$_2$OH), 2.22 (2 H, m, CH$_2$CNH$_3$), and 1.55 (8 H, m, 4 × CH$_2$).

Similarly prepared were the following. *Ethyl* 3-*ethylpent*-2-*enoate* (56%) from pentan-3-one, b.p. 52—54 °C (4 Torr) (Found: C, 68.9; H, 10.5. $C_9H_{16}O_2$ requires C, 69.2; H, 10.3%). G.l.c. (25% methyl silicone gum, 110 °C) showed the presence of a little impurity (*ca.* 3%); $\nu_{max.}$(liquid film) 1 710 (C=O), 1 640 (C=C), 1 270, 1 145 (C–O), and 865 (C=CH) cm^{-1}; δ(CDCl$_3$)[b] 5.64 (1 H, s, C=CH), 4.17 (2 H, q, *J* 7 Hz, CO$_2$CH$_2$Me), 2.65 (2 H, q, *J* 7.5 Hz, CH$_2$Me), 2.22 (2 H, q, *J* 7.5 Hz, CH$_2$Me), 1.28 (3 H, t, *J* 7 Hz, CO$_2$CH$_2$Me), and 1.08 (6 H, t, *J* 7.5 Hz, CH$_2$Me).

3-*Ethylpent*-2-*en*-1-*ol* (**7c**). This was prepared in an analogous manner to the alcohol (**7d**) above and was obtained in 60% yield, b.p. 60 °C (4 Torr) (Found: C, 73.1; H, 12.5. $C_7H_{14}O$ requires C, 73.7; H, 12.3%). G.l.c. (25% methyl silicone gum, 140 °C) showed the product to be pure; $\nu_{max.}$(liquid film) 3 300 (OH), 1 600 (C=C), and 1 000 cm^{-1} (CO); δ(CDCl$_3$)[b] 6.4 (1 H, t, *J* 7 Hz C=CH), 4.19 (2 H, d, *J* 7 Hz, CH$_2$OH), 2.12 (2 H, q, *J* 7.5 Hz, CHH$_2$Me), 2.09 (2 H, q, *J* 7.5 Hz, CH$_2$Me), 1.71 (1 H, s, CH$_2$OH), and 1.02 (6 H, m, CH$_2$Me).

3-*Chloro*-3-*ethyl*-2-*nitrosopentan*-1-*ol* (**8c**). This was prepared using the method described for (**8d**) above to give the *dimer* in 36% yield, m.p. 110 °C (Found: C, 47.2; H, 7.9; Cl, 20.2; N, 7.8. $C_{14}H_{28}Cl_2N_2O_4$ requires C, 46.8; H, 7.8; Cl, 19.8; N, 7.8%); $\lambda_{max.}$(KCl): 3 250 (OH), 1 060 (CO), and 775 cm^{-1} (CCl); δ(CDCl$_3$)[b] 6.22 (1 H, dd, *J* 3.5 Hz, CHCH$_2$OH), 4.18 (2 H, m, CH$_2$OH), 2.19 (1 H, br s, CH$_2$OH), 1.9 (4 H, m, CH$_2$Me), and 1.05 (6 H, t, CH$_2$Me).

3-*Amino*-3-*ethyl*-1-*hydroxypentan*-2-*one oxime hydrochloride* (**9c**). This was prepared using the method described for (**9d**) above in 46% yield, m.p. 182—184 °C (Found: C, 42.8; H, 8.8; Cl, 18.2; N, 14.2. $C_7H_{17}ClN_2O_2$ requires C, 42.8; H, 8.7; Cl, 18.0; N, 14.2%); $\nu_{max.}$(KCl) 3 470 (OH), 3 100—3 300 (NH), and 1 665 (CN) cm^{-1}; δ(D$_2$O)[b] 4.3 (2 H, s, CH$_2$OH), 1.94 (4 H, q, *J* 7.5 Hz, CH$_2$Me), and 0.89 (6 H, t, *J* 7.5 Hz, CH$_2$Me).

Ethyl 3-*Methyl*-5-*phenylpent*-2-*enoate*.—Triethyl phosphonoacetate (74.7 g) was added dropwise at 30 °C to a slurry of 80% sodium hydride (10 g) in dry toluene (200 ml) under a stream of dry nitrogen. The mixture was stirred for a further 0.5 h at room temperature. Benzylacetone (39.3 g) was added dropwise over 1 h and the resulting solution was stirred at 70 °C for 1 h to give a gelatinous precipitate. The mixture was cooled, diluted with water (500 ml), and extracted with ether (3 × 200 ml). The combined extracts were dried (Na$_2$SO$_4$) and evaporated at room temperature. The remaining solvent (toluene) was removed by fractional distillation at atmospheric pressure and the residue distilled at reduced pressure on a short column. The *product* (52 g, 90%) had b.p. 102—108 °C (0.2 Torr) (Found: C, 77.3; H, 8.4. $C_{14}H_{18}O_2$ requires C, 77.05; H, 8.3%); $\nu_{max.}$(liquid film) 2 963, 1 710 (CO), 1 647 (C=C), 1 600 (ArC=C), and 1 220 and 1 140 cm^{-1}; δ(CCl$_4$)[b] 6.99 (5 H, m, Ar), 5.50 (1 H, br s, C=CH), 3.98 (2 H, q, *J* 7 Hz, OCH$_2$Me), 2.8—2.2 (4 H, m, CH$_2$CH$_2$Ph), 2.14 (3 H, s, C=CMe), and 1.20 (3 H, t, *J* 7 Hz, CH$_2$Me).

G.l.c. on Apiezon at 170 °C showed two peaks in the ratio 1:3 (R_t 4.6 and 6 min respectively) corresponding to the *cis*- and *trans*-isomers.

3-*Methyl*-5-*phenylpent*-2-*en*-1-*ol* (**7e**).—A stirred solution of ethyl 3-methyl-5-phenylpent-2-enoate (50 g) in dry ether (300 ml) was cooled to 0 °C under a stream of dry nitrogen. A slurry of lithium aluminium hydride (5.25 g) in ether (80 ml) was added portionwise, the temperature being maintained at less than 8 °C. The mixture was stored overnight at room temperature. Saturated aqueous sodium sulphate was then added dropwise with stirring until the grey suspension changed into a solid white precipitate. The solid was removed by filtration and washed well with ether. The combined organic extracts were washed with brine (100 ml), dried (Na$_2$SO$_4$), and evaporated under reduced pressure. The residue was distilled through a short column to give the *alcohol* (32 g, 80%) as a colourless liquid, b.p. 108—112 °C/0.5 Torr; $\nu_{max.}$(liquid film): 3 320 (OH), 1 668 (C=C), 1 603 (ArC=C), and 1 450 cm^{-1}; δ(CCl$_4$)[b] 5.24 (1 H, t, *J* 7 Hz, C=CH), 4.93 (5 H, s, Ar), 3.94 (2 H, d, *J* 7 Hz, CH$_2$OH), 3.80 (1 H, s, OH), 2.7—2.1 (4 H, m, CH$_2$CH$_2$Ph), and 1.69 (3 H, s, C=CMe).

G.l.c. on Apiezon at 160 °C showed one peak, R_t 5.04 min.

The title alcohol formed a 3,5-dinitrobenzoyl derivative in good yield which recrystallised from methanol as cream *needles*, m.p. 58—60 °C. (Found: C, 61.7; H, 5.3; N, 7.6. $C_{19}H_{18}N_2O_6$ requires C, 61.6; H, 4.9; H, 5.0; N, 7.6%).

3-*Chloro*-3-*methyl*-2-*nitroso*-5-*phenylbutanol* (**8e**).—Concentrated hydrochloric acid (9.5 ml) was added dropwise over 0.5 h to a solution of 3-methyl-5-phenylpent-2-en-1-ol (**7e**) (9.45 g) in a mixture of pentyl nitrite (6.45 g) and acetic acid (21 ml) at 0 °C. The mixture was then cooled in a solid CO_2–acetone bath for 10 min and again allowed to warm to 0 °C. Ice-cold methanol (30 ml) was added, the mixture was stirred, and the white precipitate was collected by filtration, washed well with cold methanol and dried. The filtrates were stored at 0 °C overnight to yield a second crop of crystals. The product (3.4 g, 26%) was pure enough for subsequent reactions but could be recrystallised from methanol to give the *nitroso chloride dimer* as needles, m.p. 115—116 °C (Found: C, 59.3; H, 6.8; Cl, 14.7; N, 5.8. $C_{24}H_{32}Cl_2N_2O_4$ requires C, 59.6; H, 6.6; Cl, 14.7; N, 5.8%); $\nu_{max.}$(KBr) 3 400 (OH), 1 600 (ArC=C), 1 450, and 1 200 cm^{-1}.

3-Amino-2-hydroxyimino-3-methyl-5-phenylbutanol Hydrochloride (**9e**).—A suspension of the foregoing nitroso chloride (**8e**) (3 g) in methanolic ammonia (100 ml) was stirred at room temperature for 3 days. The resulting solution was evaporated to give the title compound as a foam which failed to crystallise; $\nu_{max.}$(film): 3 300, 1 600, 1 495, 1 450, 1 385, and 1 020 cm^{-1}; δ[$(CD_3)_2SO$][b] 7.10 (5 H, s, Ar), 4.39, 4.34 (2 H, 2 s, CH_2OH *syn* and *anti*), 2.7—2.1 (4 H, m, CH_2CH_2Ph), and 1.58 (3 H, s, Me).

1-Chloro-1-methyl-2-nitrosocyclohexane[24] (**8g**).—Concentrated hydrochloric acid (10 ml) was added dropwise over a period of 30 min to a stirred mixture of 1-methylcyclohexene (10 ml) and isopentyl nitrite (10 ml) cooled in an acetone–solid CO_2 bath (*ca.* −78 °C). Following the addition, stirring was continued for a further 1.5 h. Ice cold methanol (20 ml) was added to the resulting green paste and the mixture was filtered and washed with cold methanol to give the *nitroso chloride dimer* (5.1 g, 33%) as a white powder (Found: C, 52.3; H, 7.7; Cl, 22.0; N, 8.7. $C_{14}H_{24}Cl_2N_2O_2$ requires C, 52.2; H, 7.45; Cl, 22.0; N, 8.65%); $\nu_{max.}$(KCl) 3 030, 2 930, and 970 cm^{-1}; δ($CDCl_3$)[b] 5.8 (1 H, m, CH), 1.78, 1.70 (3 H, 2 s, Me), and 2.5—1.2 (8 H, br m, ring CH).

2-Amino-2-methylcyclohexanone Oxime Hydrochloride (**9g**).—1-Chloro-1-methyl-2-nitrosocyclohexane (**8g**) (5.1 g) was stirred overnight in saturated methanolic ammonia (100 ml). The volatile material was removed under reduced pressure, the resulting oil dissolved in a small quantity of water, and the solution adjusted to pH 7 by the dropwise addition of concentrated hydrochloric acid. The water was removed under reduced pressure and the residue was triturated with hot toluene. The resulting precipitate was removed by filtration and crystallised by dissolution in the minimum volume of hot ethanol and addition of a large volume of acetone to give the *amino oxime hydrochloride* (3.3 g, 59%) as colourless crystals, m.p. 219—220 °C (Found: C, 46.3; H, 8.6; Cl, 20.15; N, 14.7. $C_7H_{15}ClN_2O$ requires C, 47.05; H, 8.4; Cl, 19.9; N, 15.7%); δ(D_2O)[b] 3.25 (2 H, m, H-6), 1.34 (3 H, s, Me), and 1.70 (6 H, br m, ring H).

1-Chloro-1-methyl-2-nitrosocyclopentane (**8f**). This was prepared in the same manner as the cyclohexyl analogue (**8g**) in 29% yield, m.p. 72—74 °C (Found: C, 48.6; H, 4.6; Cl, 24.3; N, 9.4. $C_6H_{10}ClNO$ requires C, 48.8; H, 6.8; Cl, 24.1; N, 9.5%); $\nu_{max.}$(KCl) 3 000, 2 970, and 1 227 cm^{-1}; δ($CDCl_3$)[b] 5.66 (1 H, m, H-2), 2.7—1.5 (6 H, m), and 1.79 (3 H, m). This compound was unstable to storage.

2-Amino-2-methylcyclopentanone oxime hydrochloride (**9f**). This was prepared following the method for the cyclohexyl analogue (**9g**) in 80% yield, m.p. 222—223 °C (Found: C, 43.6; H, 7.9; Cl, 21.4; N, 17.2. $C_6H_{13}ClN_2O$ requires C, 43.8; H, 7.9; Cl, 21.6; N, 17.1%); $\nu_{max.}$(KCl) 3 380 and 2 980 cm^{-1}; δ(D_2O)[b] 2.76 (2 H, m), 2.01 (4 H, m), and 1.50 (3 H, s).

Synthesis via *Nitroalkanols*

3-Methyl-3-nitrobutan-2-ol (**10a**), 2-methyl-2-nitropentan-3-ol (**10b**), and 2-methyl-2-nitrohexan-3-ol (**10c**) were all prepared as described previously.[15]

3-Methyl-3-nitrobutan-2-one (**11a**).—A mixture of 3-methyl-3-nitrobutan-2-ol (**10a**) (10 g), sodium dichromate (15 g), and water (10 ml) was treated portionwise with concentrated sulphuric acid (9.8 ml) and water (4.6 ml) over 6 h, the internal temperature being kept at 10—20 °C. After an additional 2 h at room temperature, water (30 ml) was added and the solution extracted with ether (3 × 50 ml). The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated to give a residual pale yellow oil which on fractional distillation gave the nitro ketone as a colourless oil, b.p. 62—63 °C/14 Torr which solidified with time; m.p. 31—32 °C (7.5 g); $\nu_{max.}$($CHCl_3$) 1 730 (CO), 1 540, and 1 455 (NO_2); δ($CDCl_3$)[b] 2.25 (3 H, s, Me), and 1.76 (6 H, s, $(Me)_2C$).

The semicarbazone was prepared by dissolving the nitro ketone (**3g**) in ethanol (20 ml), adding the solution portionwise to a warm solution of semicarbazide hydrochloride (3 g) and sodium acetate (4 g) in water (25 ml), and warming the mixture on a steam-bath for 30 min. The ethanol was removed under reduced pressure and the resultant precipitate was filtered off, washed with water, and recrystallised from ethanol to give the *semicarbazone* as colourless needles m.p. 161—162 °C (1.9 g) (Found: C, 38.6; H, 6.2; N, 29.7. $C_6H_{12}N_4O_3$ requires C, 38.3; H, 6.4; N, 29.8%).

3-Amino-3-methylbutan-2-ol.—3-Methyl-3-nitrobutan-2-ol (5 g) was dissolved in methanol (300 ml) and hydrogenated over freshly prepared Raney Nickel (2.0 g) at room temperature and 4 atm for 5 h until uptake of hydrogen was complete. The catalyst was removed by filtration and the solvent evaporated to give the amino alcohol as a colourless oil (3.6 g); δ($CDCl_3$)[b] 3.6 (1 H, q, C*H*), 1.2 (6 H, s, Me_2C), and 1.5—1.2 (3 H, m, CH*Me*). The *picrate* was prepared by adding saturated picric acid in ethanol to a solution of 3-amino-3-methylbutan-2-ol in ethanol; the yellow solid recrystallised from ethanol as yellow needles, m.p. 164—166 °C (Found: C, 40.2; H, 5.4; N, 15.4. $C_{11}H_{16}N_4O_8 \cdot \frac{1}{2}C_2H_5OH$ requires C, 40.5; H, 5.3; N, 15.7%); δ(D_2O)[b] 8.91 (2 H, s, Ar), 5.9 (1 H, q, *J* 6 Hz, CH), 1.35 (6 H, s, Me_2C), and 1.25 (3 H, d, *J* 6 Hz, Me).

3-Benzamido-3-methylbutan-2-ol.—3-Amino-3-methylbutan-2-ol (6.1 g) was dissolved in benzene (120 ml) and treated with anhydrous sodium carbonate (16 g) and cooled to 10 °C. The mixture was treated with benzoyl chloride (9.2 g) in benzene (30 ml) the temperature being kept at 10 °C. After 3 h the reaction mixture was kept at room temperature for 2 h, and then refluxed for 30 min, filtered hot, and the solid extracted with hot benzene (2 × 100 ml). The combined filtrates were evaporated to 100 ml and cooled. The colourless crystalline solid was collected and recrystallised from benzene as colourless needles, m.p. 118—120 °C (5 g); $\nu_{max.}$($CHCl_3$) 3 420 (OH, free), 3 200—3 400 (OH, NH, bonded), 1 650 (CONH), 1 600 (Ar), and 1 560 (CONH) cm^{-1}; δ($CDCl_3$) 7.9—7.4 (5 H, m, Ar), 3.8 (1 H, q, *J* 6 Hz, C*H*Me), 1.52, 1.40 (6 H, 2 s, Me_2C), and 1.20 (3 H, d, *J* 6 Hz, CH*Me*).

3-Benzamido-3-methylbutan-2-one.—Chromium trioxide (3 g) was added to a vigorously stirred, cooled solution of pyridine (35 ml) over 15 min. 3-Benzamido-3-methylbutan-2-ol (2.02 g) in anhydrous pyridine (4 ml) was added all at once and the mixture stirred at 0 °C for 30 min and then at room temperature for a further 22 h. The reaction mixture was poured into water (100 ml) and extracted with ether (3 × 50 ml). The combined extracts were washed with water and brine, dried, and evaporated to give the required ketone as a white powder which was recrystallised from benzene–light petroleum as colourless needles, m.p. 124—125 °C (Found: C, 69.8; H, 7.0; N, 7.0. $C_{12}H_{15}NO_2$ requires C, 70.2; H, 7.3; N, 6.8%); $\nu_{max.}$($CHCl_3$) 3 400 (NH), 1 715 (CO), 1 655, 1 560 ($CONH_2$), and 1 600 (Ar); δ($CDCl_3$)[b] 7.9—7.4 (5 H, m, Ar), 2.25 (3 H, s, MeCO), and 1.6 (6 H, s, Me_2C).

3-Amino-3-methylbutan-2-one Hydrochloride (**12a**).—3-Benzamido-3-methylbutan-2-one (1 g) was suspended in hydrochloric acid (20%, 10 ml) and refluxed for 8 h. The solution was cooled and the precipitated benzoic acid filtered off. The filtrate was evaporated and the residue was treated with water (2 ml)

and filtered to remove a further quantity of benzoic acid. The filtrate was evaporated and the residue triturated thrice with cold ethanol (3 × 5 ml); each time the mixture was filtered, and the filtrate evaporated to leave a residue which was recrystallised from ethanol–ether as colourless needles (500 mg), m.p. 212—214 °C, $\nu_{max.}$(Nujol) 3 400 (NH) and 1 730 cm^{-1} (CO); $\delta(CDCl_3)$[b] 4.78 (3 H, br, NH_3), 2.4 (3 H, s, *Me*CO), and 1.65 (6 H, s, Me_2C).

2-*Methyl*-2-*nitropentan*-3-*one* (**11b**).—2-Methyl-2-nitropentan-3-ol (119 g), sodium dichromate (268 g), and water (190 ml) were mixed and cooled in an ice–salt bath. Pre-cooled concentrated sulphuric acid (196 g) was added slowly over 1 h to the reaction mixture, the temperature being kept below 15 °C. After the addition was complete, the reaction mixture was stirred at room temperature for 2.5 h, and water (500 ml) was added. The solution was extracted with ether and dried (Na_2SO_4). The ether was removed under reduced pressure and the residue (113 g) distilled to give the *nitro ketone* (96 g, 82%), b.p. 35 °C/0.2 Torr (Found: C, 49.2; H, 4.6; N, 9.6. $C_6H_{11}NO_3$ requires C, 49.6; H, 7.6; N, 9.7%).

2-*Amino*-2-*methylpentan*-3-*one Hydrochloride* (**12b**).—Palladium–charcoal (10%; 5 g) was placed in a hydrogenation flask and covered by 2-methyl-2-nitropentan-3-one (**11b**) (14.5 g) and isopropyl alcohol (100 ml). To this was added isopropyl alcohol (20 ml) saturated with hydrogen chloride and the mixture was hydrogenated at room temperature and atmospheric pressure until uptake of hydrogen was complete. The catalyst was filtered off and the isopropyl alcohol removed under reduced pressure to give the crude amino ketone hydrochloride as a pale green solid (10.9 g, 70%). Recrystallisation (twice) from dry chloroform–light petroleum afforded a colourless hygroscopic solid (5.5 g), m.p. 140—142 °C. Owing to the hygroscopic nature of the material an elemental analysis was not obtained.

2-*Methyl*-2-*nitrohexan*-3-*one* (**11c**).—Using the procedure described above for the synthesis of 2-methyl-2-nitropentan-3-one, 2-methyl-2-nitrohexan-3-ol afforded the title compound after distillation as a colourless oil (87%) b.p. 91 °C/18 Torr.

2-*Amino*-2-*methylhexan*-3-*one Hydrochloride* (**12c**).—2-Methyl-2-nitrohexan-3-one (15.9 g, 0.1 mole) was dissolved in absolute alcohol (100 ml) and added to palladium–charcoal (10%, 5 g) in a hydrogenation flask. Ethanolic hydrogen chloride (20 ml) was added and the mixture hydrogenated until uptake of hydrogen was complete (*ca.* 8.5 days). The catalyst was filtered off and the ethanol removed under reduced pressure to leave a creamy-white residue. This was dissolved in the minimum volume of warm acetone (*ca.* 10 ml); light petroleum was then added dropwise to initiate crystallisation. The mixture was cooled in an alcohol–solid CO_2 bath to complete precipitation of the product. The amino ketone hydrochloride was filtered off and dried under reduced pressure (12.8 g, 78%), m.p. 126—127 °C.

Synthesis of Pyrimidines and Pteridines

2-*Amino*-6-*chloro*-5-*nitropyrimidin*-4(3H)-*one*.—2-Amino-6-chloropyrimidin-4(3*H*)-one (5 g) was dissolved in concentrated sulphuric acid (6 ml) at 40 °C and treated portionwise, with stirring, with fuming nitric acid (5.4 ml). The resulting solution was stirred for 1 h and added to crushed ice (20 g). The solid obtained was collected by filtration, washed with ice–water (25 ml), cold ethanol (25 ml), and cold ether and then dried over phosphorus pentaoxide to give the chloronitropyrimidine (5 g, 77%), m.p. 365 °C (lit.,[24] 360 °C); $\nu_{max.}$(KCl) 3 590, 3 470, 1 680, and 1 580 cm^{-1}; $\lambda_{max.}$(pH 13) 366 and 275 nm; $\lambda_{max.}$(*p*H 1) 289 nm.

2-*Amino*-6-(4-*hydroxy*-3-*hydroxyimino*-2-*methylbutan*-2-*ylamino*)-5-*nitropyrimidin*-4(3H)-*one* (**13a**).—3-Amino-3-methyl-2-hydroxyiminobutan-1-ol hydrochloride (**9a**) (2.5 g) was dissolved in ethanol (16 ml) and treated with 2-amino-6-chloro-5-nitropyrimidin-4(3*H*)-one (2.8 g) and triethylamine (2.8 g). The mixture was stirred at room temperature for 2 h, heated under reflux for 4 h, and then allowed to stand at room temperature for 8 h. The reaction mixture was reheated, filtered whilst hot, and the solid residue washed with hot ethanol. From the ethanol solution was isolated a pale yellow powder which was recrystallised from boiling water to give the *title compound* as an off-white powder (1.5 g) (Found: C, 37.0; H, 5.3; N, 28.2. $C_9H_{14}N_6O_5 \cdot \frac{1}{2}H_2O$ requires: C, 36.6; H, 5.1; N, 28.4%); $\delta[(CD_3)_2SO]$[b] 7.3, 4.9, 3.4 (5 H, br, exch. with D_2O, OH, NH), 4.4 (2 H, d, CH_2OH), and 1.75 (6 H, s, Me).

7,8-*Dihydro*-6-*hydroxymethyl*-7,7-*dimethylpteridin*-4(3H)-*one* (**14a**).—The above pyrimidine (**13a**) was dissolved in 0.1M-sodium hydroxide (3 ml) with warming on a steam-bath. The warm solution was treated portionwise with sodium dithionite until the yellow colour was discharged. On cooling, a white solid precipitated which was filtered off, washed with water, and dried to give the *pteridine* as a pale yellow powder (40 mg) (Found: C, 48.1; H, 5.7; N, 31.5. $C_9H_{13}N_5O_2$ requires C, 48.4; H, 5.8; N, 31.4%); $\lambda_{max.}$(0.1M NaOH) 324 and 281 nm (ε 9 200 and 10 000 $dm^3\ mol^{-1}\ cm^{-1}$) (0.1M HCl) 352 and 277 nm (ε 4 000 and 4 700 $dm^3\ mol^{-1}\ cm^{-1}$); δ(NaOD)[b] 1.5 (2 × Me).

2-*Amino*-6-(2-*benzyl*-4-*hydroxy*-3-*oxobutan*-2-*ylamino*)-5-*nitropyrimidin*-4(3H)-*one Semicarbazone* (**13b**; X = N·NHCONH$_2$).—The amino ketone hydrochloride semicarbazone (**2b**) (7.0 g, 24.5 mmol), 2-amino-6- chloro-5-nitropyrimidin-4(3*H*)-one (4.51 g, 24.0 mmol) and freshly distilled triethylamine (6.8 ml, 49 mmol) were refluxed in magnesium ethoxide-dried ethanol (450 ml) for 22 h. The reaction mixture was cooled and evaporated to 180 ml to precipitate the pyrimidinylamino ketone semicarbazone (**13b**) as a pale yellow solid (4.68 g, 48%), m.p. 216—218 °C; $\lambda_{max.}$ 3 300 (NH_2), 1 592 (NCN), 1 570, 1 295 (NO_2), and 725 cm^{-1} (Ph); $\delta[(CD_3)_2SO]$[a] 9.36 (1 H, s, OH), 7.19 (5 H, m, Ph), 6.92 (3 H, m, H_2NHN), 6.35 (2 H, s, H_2NO), 5.94 (1 H, s, NHO), 4.48 (2 H, s, CH_2OH), 4.31 (1 H, s, NH), 4.04 (1 H, d, *J* 14 Hz, $PhCH_2$), 3.12 (1 H, d, *J* 14 Hz, $PhCH_2$), and 1.80 (3 H, s, Me).

2-*Amino*-6-(2-*benzyl*-4-*hydroxy*-3-*oxobutan*-2-*ylamino*)-5-*nitropyrimidin*-4(3H)-*one* (**13b**).—The pyrimidinylamino ketone semicarbazone (4.2 g, 10.39 mmol) was refluxed for 8 min in 2M-hydrochloric acid (75 ml). The solution was cooled, filtered, and neutralised with ammonia (*d* 0.880), added dropwise with stirring, to precipitate the pyrimidinylamino ketone (**2c**) as a yellow white solid. This was washed with water, ethanol, and ether and recrystallised from aqueous ethanol to afford the *ketone* (**13b**) as a yellow-white amorphous solid (3.59 g, 97%), m.p. 195—197 °C (Found: *m/z* 316.1042. $C_{14}H_{14}N_5O_4$ requires *m/z* 316.1046); $\lambda_{max.}$(0.1M HCl) 207, 229infl and 326 nm (ε 30 800, 19 900 and 13 120 $dm^3\ mol^{-1}\ cm^{-1}$); $\nu_{max.}$ 3 441 (H_2N and OH), 1 691 (CO), 1 571, 1 290 (NO_2), and 724 cm^{-1} (Ph); $\delta[(CD_3)_2SO]$ 9.64 (1 H, s, OH), 7.20 (5 H, m, Ph), 7.78—7.11 (3 H, m, H_2NNH), 4.41 (2 H, s, CH_2OH), 4.05 (1 H, s, NH), 3.44 (1 H, *J* 12 Hz, $PhCH_2$), 3.14 (1 H, d, *J* 12 Hz, $PhCH_2$), and 1.49 (3 H, s, Me).

2-*Amino*-7-*benzyl*-7,8-*dihydro*-6-*hydroxymethyl*-7-*methylpteridin*-4(3H)-*one* (**14b**).—The pyrimidinylamino ketone (**13b**) (0.5 g, 1.44 mmol) was boiled in water (40 ml) and treated with

solid sodium dithionite (0.98 g, 5.62 mmol) in small portions over 1 h. Boiling was then continued until no trace of the pyrimidinylamino ketone (**13b**) was detectable by u.v. spectroscopy. The mixture was then allowed to cool to room temperature to complete the separation of the product, which was filtered off and washed with water, ethanol, and water. It was then purified by dissolution in 2M-hydrochloric acid, filtration and dropwise addition of ammonia (*d* 0.880) to pH 8.0 to precipitate the *pteridine* (**14b**) as a yellow-orange solid which was dried over phosphorus pentaoxide *in vacuo* (0.39 g, 90%), m.p. (decomp.) >360 °C (Found: C, 58.6; H, 5.6; N, 22.9%; *M* − 0.5H_2O, *m/z* 299.1384. $C_{15}H_{17}N_5O_2$·0.5H_2O requires C, 58.4; H, 5.7; N, 22.9%; *M* − 0.5 H_2O, *m/z* 299.1382); $\lambda_{max.}$(0.1M HCl) 207, 259, 279, and 359 nm (ε 23 320, 17 100, 8 300, and 6 596 dm^3 mol^{-1} cm^{-1}); $\nu_{max.}$ 3 450 (H_2O of crystallisation), 1 668—2 600 (CN), and 726 cm^{-1} (Ph); δ[$(CD_3)_2SO$] 7.18 (5 H, m, ArH), 6.78 (1 H, s, NH), 6.34 (2 H, s, NH_2), 4.64 (1 H, s, OH), 4.10 (2 H, s, CH_2OH), 3.71 (1 H, s, NH), 3.32 (1 H, s, ½H_2O), 3.00 (1 H, d, *J* 9 Hz, PhCH_2), 2.75 (1 H, d, *J* 9 Hz, PhCH_2), and 1.34 (3 H, s, Me).

2-*Amino*-6-[4-*hydroxy*-3-*hydroxyimino*-2-(2-*phenylethyl*)-*butan*-2-*ylamino*]-5-*nitropyrimidin*-4(3H)-*one* (**13c**).—A suspension of 3-chloro-3-methyl-2-nitroso-5-phenylbutanol (3 g) in methanolic ammonia (100 ml) was stirred at room temperature for 3 days and the resulting colourless solution evaporated to a foam. Absolute ethanol (100 ml), triethylamine (2.5 g), and 2-amino-6-chloro-5-nitropyrimidin-4(3*H*)-one (3.5 g) were added to the residue and the mixture was heated under reflux for 4.5 h. The reaction mixture was stored overnight at 0 °C, filtered, and the filtrate evaporated to give a clear brown gum. The residue was triturated with cold water (100 ml), stored at room temperature for 1 h, and the resulting solid collected by filtration, washed with water, and dried. The product (3.6 g, 75%) reprecipitated from aqueous sodium hydroxide–acetic acid–charcoal to give the *nitropyrimidine* as a pale yellow powder, decomp. from 200 °C (Found: C, 51.2; H, 5.4; N, 22.4. $C_{16}H_{20}N_6O_5$ requires C, 51.1; H, 5.4; N, 22.3%); $\lambda_{max.}$(pH 14) 348 (ε 15 700), (pH 1) 336 nm (ε 10 800 dm^3 mol^{-1} cm^{-1}); $\nu_{max.}$(KBr) 3 220, 1 680, 1 570, and 1 430 cm^{-1}; δ[$(CD_3)_2SO$][b] 7.00 (5 H, s, Ar), 4.20 (2 H, s, CH_2O), 2.30 (4 H, m, CH_2CH_2Ph), and 1.73 (3 H, s, Me).

2-*Amino*-7,8-*dihydro*-6-*hydromethyl*-7-*methyl*-7-(2-*phenylethyl*)*pteridin*-4(3H)-*one* (**14c**).—A solution of 2-amino-6-[4-hydroxy-3-hydroxyimino-2-(2-phenylethyl)butan-2-ylamino]-5-nitropyrimidin-4(3*H*)-one (**13c**) (1 g) in 0.1M-aqueous sodium hydroxide (20 ml) at 100 °C was treated portionwise with sodium dithionite. The solution turned from yellow through orange to pale yellow. The mixture was cooled and adjusted to pH 8 with dilute hydrochloric acid. The resulting solid (590 mg), 71%), reprecipitated from aqueous sodium hydroxide/hydrochloric acid to give the *pteridine* hemihydrate as a pale yellow powder, decomp. from 160 °C (Found: C, 59.4; H, 6.2; N, 21.6. $C_{16}H_{19}N_5O_2$·0.5H_2O requires C, 59.6; H, 6.2; N, 21.75%); $\lambda_{max.}$(pH 14) 236, 281, and 325 (ε 13 440, 6 500, and 4 880); (pH 1) 261 and 364 nm (ε 12 030 and 3 610 dm^3 mol^{-1} cm^{-1}); $\nu_{max.}$(KBr) 3 140, 1 600, 1 545, 1 450, and 1 378 cm^{-1}; δ[$(CD_3)_2SO$][b] 7.08 (5 H, s, Ar), 4.10 (2 H, s, CH_2O), 2.7—1.6 (4 H, m, CH_2CH_2Ph), and 1.31 (3 H, s, Me).

2-*Amino*-6-[1-(2-*hydroxy*-1-*hydroxyiminoethyl*)*cyclohexyl*-*amino*]-5-*nitropyrimidin*-4(3H)-*one* (**13e**).—A suspension of 2-amino-6-chloro-5-nitropyrimidin-4(3*H*)-one (2.3 g) in dry ethanol (50 ml), was treated with the oxime hydrochloride (**9d**) (2.5 g) and dry triethylamine (2.7 g) and the mixture was refluxed for 7 h. The reaction mixture was then filtered and the solid washed with hot ethanol. The solvent was removed from the filtrate and the resulting yellow oil was triturated with cold water giving a yellow solid which on recrystallisation from water (charcoal) gave the *pyrimidine* (**13e**) (1.85 g, 47%) as an off-white powder, m.p. >300 °C (decomp.) (Found: C, 44.4; H, 5.8; N, 26.0. $C_{12}H_{18}N_6O_5$ requires C, 44.1; H, 5.6; N, 25.8%); $\lambda_{max.}$(pH 1) 334 (ε 14 290), (pH 13) 347 and 221 nm (ε 18 980 and 15 150 dm^3 mol^{-1} cm^{-1}); δ[$(CD_3)_2SO$][b] 9.88 (1 H, s, NH), 9.48 (1 H, s, NH), 6.95 (2 H, br s, NH_2), 4.69 (1 H, m, OH), 4.20 (2 H, m, CH_2OH), 2.36 (2 H, m, CH_2), and 1.56 (8 H, m, CH_2).

2-*Amino*-6-(1,1-*diethyl*-3-*hydroxy*-2-*hydroxyiminopropyl*-*amino*)-5-*nitropyrimidin*-4(3H)-*one* (**13d**). This was prepared in the same manner as the preceding compound. Recrystallisation from water (charcoal) gave the *nitropyrimidine oxime* (1.3 g, 30%) as a fine white solid, m.p. >250 °C (decomp.) (Found: C, 42.4; H, 5.8; N, 27.0. $C_{11}H_{18}N_6O_5$ requires C, 42.0; H, 5.7; N, 26.7%). $\lambda_{max.}$(pH 1) 335, 236sh, and 218 (ε 13 490 and 18 830) (pH 13) 347 and 222 nm (ε 16 220 and 16 430 dm^3 mol^{-1} cm^{-1}); δ(CD_3OD)[b] 4.26 (2 H, s, CH_2OH), 2.7 (2 H, m, CH_2Me), 1.88 (2 H, m, CH_2Me), and 0.72 (6 H, t, *J* 7 Hz, CH_2*Me*).

2-*Amino*-7,8-*dihydro*-6-*hydroxymethylpteridine*-7-*spirocyclo*-*hexan*-4(3H)-*one* (**14e**).—The pyrimidine (**13e**) (500 mg) was dissolved in the minimum of 0.1M-sodium hydroxide by warming on a steam-bath. Sodium dithionite was added portionwise until an almost colourless solution was obtained. On cooling, the dihydropteridine separated and was filtered off and purified by dissolution in 2M-hydrochloric acid and precipitation by the addition of ammonia (*d* 0.880) to pH 8. With time the *dihydropteridine* (150 mg, 38%) was obtained as a pale yellow crystalline solid, m.p. >300 °C (decomp.) (Found: C, 54.6; H, 6.4; N, 26.6. $C_{12}H_{17}N_5O_2$ requires C, 54.7; H, 6.5; N, 26.60%); $\lambda_{max.}$(pH 1), 353, 272sh, and 256 (ε 6 060, 7 550, and 15 100), (pH 13) 322, 281, and 232 nm (ε 6 800, 8 310, and 15 620 dm^3 mol^{-1} cm^{-1}); δ(NaOD)[b] 4.28 (2 H, s, CH_2OH), and 1.63 (10 H, m, 5 CH_2).

2-*Amino*-7,7-*diethyl*-7,8-*dihydro*-6-*hydroxymethylpteridin*-4(3H)-*one* (**14d**). This was prepared in the same way as the preceding compound although no solid product was obtained either on cooling or on adjusting the pH. In order to separate the product from inorganic material, the solution was evaporated and the product extracted with ethanol; the inorganic material was then filtered off. This extraction was repeated and the combined extracts were evaporated to dryness under reduced pressure. The residue was dissolved in the minimum quantity of water and placed on a column of Amberlite CG-50 ion exchange resin (2.5 × 28 cm) in its H^+ form. Elution with water gave two main fluorescent bands. Evaporation of the solution containing the first band gave the 6-*carbaldehyde* derivative of the title compound (10 mg, 3%) as a bright orange powder (Found: *M*, *m/z* 249.1254. $C_{11}H_{15}N_5O_2$ requires *M*, *m/z* 249.1226); $\lambda_{max.}$(pH 1) 410, 279sh, 268, and 258 (ε 5 270, 1 740, 10 840, and 11 460), (pH 13) 446, 330, and 268 (ε 6 960, 2 940, and 10 840 dm^3 mol^{-1} cm^{-1}). The second band gave the required 7,8-*dihydropteridine* (160 mg, 45%) as a bright yellow powder, m.p. >300 °C (decomp.) (Found: C, 52.8; H, 6.1; N, 26.0%; *M*, *m/z* 251.1381. $C_{11}H_{17}N_5O_2$ requires C, 52.6; H, 6.8; N, 27.9%; *M*, *m/z* 251.1382); $\lambda_{max.}$(pH 1) 374, 272sh, and 255 (ε 4 800, 7 100, and 16 220), (pH 13) 330, 280, and 237 nm (ε 5 620, 7 170, and 15 500 dm^3 mol^{-1} cm^{-1}); δ(CD_3OD)[b] 4.15 (2 H, s, CH_2OH), 1.55 (4 H, m, CH_2Me), and 0.95 (6 H, t, CH_2*Me*).

2-*Amino*-6-(2-*hydroxyimino*-1-*methylcyclopentylamino*)-5-*nitropyrimidin*-4-(3H)-*one* (**13f**; X = NOH).—2-Amino-6-chloro-5-nitropyrimidin-4(3*H*)-one (1.5 g) and 2-amino-2-methylcyclopentanone oxime hydrochloride (13 g) in absolute

ethanol (50 ml) containing triethylamine (3 ml) were heated under reflux for 8 h during which time much of the product had precipitated. After cooling, the mixture was concentrated under reduced pressure, water (50 ml) was added, and the precipitate was removed by filtration. It was purified by dissolution in the minimum of 0.1M-sodium hydroxide solution with warming, the solution then being adjusted to pH 7 with glacial acetic acid. The *nitropyrimidine* (1.96 g, 89%) was removed by filtration, m.p. 269 °C (decomp.) (Found: C, 42.6; H, 4.85; N, 29.85% *M*, *m/z* 282.1060. $C_{10}H_{14}N_6O_4$ requires C, 42.55; H, 4.95; N, 29.85%; *M*, *m/z* 282.1076); $\lambda_{max.}$(pH 1) 330 (ε 14 300) and (pH 13) 348 nm (18 900 dm^3 mol^{-1} cm^{-1}); δ(NaOD)[b] 2.49 (2 H, m, 3′-H), 2.15 (2 H, m, 5′-H), 1.19 (2 H, m, 4′-H), and 1.52 (3 H, s, Me).

2-*Amino*-6-(1-*methyl*-2-*oxocyclopentylamino*)-5-*nitropyrimidin*-4(3H)-*one* (**13f**; X = O).—2-Amino-6-chloro-5-nitropyrimidin-4(3*H*)-one (1.5 g) and 2-amino-2-methylcyclopentanone hydrochloride (1.2 g) in absolute ethanol (50 ml) containing triethylamine (3 ml) were heated under reflux for 8 h. The mixture was cooled and concentrated under reduced pressure. Water (50 ml) was added and the precipitate was removed by filtration. This was purified by dissolution in the minimum volume of hot aqueous sodium hydroxide (0.1M) and adjusting the pH to 7 with glacial acetic acid. After cooling, the *nitropyrimidine* (1.58 g, 71%) was removed by filtration, m.p. >300 °C (decomp.) (Found: C, 44.4; H, 4.9; N, 26.5. $C_{10}H_{13}N_5O_4$ requires C, 44.7; H, 4.85; N, 26.25%); $\lambda_{max.}$(pH 1) 315 (ε 14 000) and (pH 13) 341 nm (ε 16 000 dm^3 mol^{-1} cm^{-1}); δ[$(CD_3)SO$][b] 7.6—7.0 (br, NH), 2.24 (2 H, m, 3′-H), 1.86 (4 H, m, 4′- and 5′-H), and 1.29 (3 H, s, Me).

2-*Amino*-8a,9-*dihydro*-8a-*methylcyclopenta*[*g*]*pteridin*-4(3H)-*one* (**14f**).—(*a*) 2-Amino-6-(2-hydroxyimino-1-methylcyclopentylamine)-5-nitropyrimidin-4(3*H*)-one (1.41 g) dissolved in aqueous sodium hydroxide (0.5M; 20 ml) containing 10% Pd–charcoal (200 mg) was hydrogenated at room temperature and atmospheric pressure. When the theoretical quantity of hydrogen (33 ml) had been taken up the catalyst was removed by filtration. The product was purified by dissolution in the minimum quantity of aqueous sodium hydroxide under nitrogen and adjusting the solution to pH 7 with glacial acetic acid to give the *pteridine* (346 mg, 32%) as an off-white powder, m.p. >300 °C (decomp.) (Found: C, 54.25; H, 6.05; N, 32.5%; *M*, *m/z* 219.1119. $C_{10}H_{13}N_5O$ requires C, 54.75; H, 5.95; N, 32.0%; *M*, 219.1120); $\lambda_{max.}$(pH 1.3) 352, 273sh, and 255 (ε 6 400, 7 650, and 16 000), (pH 13.2) 322 and 282 nm (ε 6 800 and 9 500).

(*b*) 2-Amino-6-(1-methyl-2-oxocyclopentylamino)-5-nitropyrimidin-4(3*H*)-one (267 mg) dissolved in aqueous sodium hydroxide (3 ml) containing 10% Pd–charcoal (40 mg) was hydrogenated as described above. The product was purified as described above to give the pteridine (88 mg, 40%).

2-*Amino*-8a,9-*dihydro*-8a-*methylcyclopenta*[g]*pteridin*-4(3H)-*one Dihydrogen Sulphite* (**14f**).—(*a*) 2-Amino-6-(1-methyl-2-oxocyclopentylamino)-5-nitropyrimidin-4(3*H*)-one (3.2 g) was dissolved in the minimum quantity of aqueous sodium hydroxide (2M) with heating on a steam-bath. Solid sodium dithionite was added portionwise until reduction was complete; further portions of aqueous sodium hydroxide (2M) being added where necessary to keep the solution basic. The mixture was adjusted to pH 7 with saturated aqueous sulphur dioxide and cooled in ice for 2 h. The resulting white precipitate was removed by filtration and purified by dissolution in the minimum volume of aqueous sodium hydroxide (0.1M) under nitrogen and adjusting the solution to pH 7 with saturated aqueous sulphur dioxide. After the mixture had been stored at 0 °C overnight the *pteridine dihydrogen sulphite* (1.5 g, 39%) was removed by filtration, m.p. >250 °C (decomp.) (Found: C, 37.9; H, 5.35; N, 22.0; S, 9.8. $C_{10}H_{15}N_5O_4S{\cdot}H_2O$ requires C, 37.6; H, 5.35; N, 21.95; S, 10.05%); $\lambda_{max.}$(pH 1.8) 355, 273sh and 255 (ε 7 460, 8 600, and 19 000), (pH 13) 322 and 282 nm (ε 8 100 and 10 600 dm^3 mol^{-1} cm^{-1}); δ(NaOD)[b] 1.95 (4 H, m, 7- and 8-H) and 1.09 (3 H, s, Me).

(*b*) 2-Amino-6-(2-hydroxyimino-1-methylcyclopentylamino)-5-nitropyrimidin-4-(3*H*)-one (500 mg) dissolved in the minimum volume of hot aqueous sodium hydroxide (2M) was reduced as described above. The mixture was neutralised with saturated aqueous sulphur dioxide and cooled to precipitate the pteridine sulphite which was collected by filtration and purified as described above (200 mg, 35%).

2-*Amino*-6-(2-*hydroxyimino*-1-*methylcyclohexylamino*)-5-*nitropyrimidin*-4(3H)-*one* (**13g**).—2-Amino-6-chloro-5-nitropyrimidin-4(3*H*)-one (2.5 g) and 2-amino-2-methylcyclohexanone oxime hydrochloride (1.9 g) in absolute ethanol (50 ml) containing triethylamine (3 g) were heated under reflux for 6 h. After cooling, the solution was concentrated under reduced pressure, water (50 ml) was added and the precipitate was removed by filtration. The material was purified by dissolving it in the minimum volume of hot 50% ammonia solution and slowly evaporating the ammonia on a hot-plate. The resulting plates of the *nitropyrimidine* (2.7 g, 69%) were removed by filtration and dried in air, m.p. >360 °C (decomp.) (Found: C, 44.9; H, 5.6; N, 28.6%; *M*, *m/z* 296.1230. $C_{11}H_{16}N_6O_4$ requires C, 44.6; H, 5.4; N, 28.4%; *M*, *m/z* 296.1233); $\lambda_{max.}$(pH 1) 330 (ε 13 500), (pH 13) 347 nm (ε 18 400 dm^3 mol^{-1} cm^{-1}); δ(NaOD) 3.0—2.6 (2 H, m, 3′-H), 2.2—1.4 (6 H, m, 4′-, 5′-, and 6′-H), and 1.57 (3 H, s, Me).

2-*Amino*-6-(1-*methyl*-2-*oxocyclohexylamino*)-5-*nitropyrimidin*-4(3H)-*one* (**13g**; X = O).—(*a*) 2-Amino-6-chloro-5-nitropyrimidin-4(3*H*)-one (1.55 g) and 2-amino-2-methylcyclohexanone hydrochloride (1.34 g) in absolute ethanol (45 ml) containing triethylamine (3 ml) were heated under reflux for 6 h. After cooling, the mixture was concentrated under reduced pressure, water (50 ml) was added, and the resulting precipitate was removed by filtration. This was recrystallised from aqueous ethanol to give the *nitropyrimidine* (1.53 g, 55%), m.p. 276—278 °C (decomp.) (Found: C, 45.5; H, 5.45; N, 24.7%; *M*, *m/z* 281.1125. $C_{11}H_{15}N_5O_4{\cdot}\frac{1}{2}H_2O$ requires C, 45.5; H, 5.5; N, 24.15%; *M*, *m/z* 281.1124). $\lambda_{max.}$(pH 1) 317 (ε 15 100), (pH 13) 345 nm (ε 20 600 dm^3 mol^{-1} cm^{-1}); δ[$(CD_3)_2SO$][b] 2.6—2.3 (2 H, m, 3′-H), 2.0—1.6 (6 H, m, 4′-, 5′-, and 6′-H), and 1.56 (3 H, s, Me).

(*b*) 2-Amino-6-(2-hydroxyimino-1-methylcyclohexylamino)-5-nitropyrimidin-4(3*H*)-one (330 mg) was heated under reflux for 3 h in hydrochloric acid (0.1M; 50 ml). The mixture was cooled, adjusted to pH 7 with dilute ammonia solution, and the solvent evaporated under reduced pressure. The residue was dissolved in the minimum quantity of hydrochloric acid (1M) and the residual crystalline material (40 mg) was removed by filtration. This was shown to be 6-(1-methyl-2-oxycyclohexylamino)-5-nitropyrimidine-2,4(1*H*,3*H*)-dione by comparison with an authentic sample. The filtrate from above was adjusted to pH 7 with strong ammonia solution and the mixture stored at 0 °C overnight. Filtration of the resultant crystalline material gave 2-amino-6-(1-methyl-2-oxycyclohexylamino)-5-nitropyrimidin-4(3*H*)-one (120 mg, 37%) identical with that prepared above.

6-(1-*Methyl*-2-*oxocyclohexylamino*)-5-*nitropyrimidin*-2,4(1H,3H)-*dione*.—2-Amino-6-(1-methyl-2-oxocyclohexylamino)-5-nitropyrimidin-4(3*H*)-one (200 mg) in hydrochloric acid (0.2M, 50 ml) was heated under reflux for 16 h. The mixture

was cooled, neutralised with dilute ammonia solution, and the solvent removed under reduced pressure. Water (20 ml) was added and the insoluble material was removed by filtration and crystallised from aqueous ethanol to give the *nitropyrimidine* (100 mg, 50%) as colourless plates, m.p. 266 °C (decomp.) (Found: C, 47.0; H, 5.0; N, 19.8. $C_{11}H_{14}N_4O_5$ requires C, 46.8; H, 4.95; N, 19.85%); $\lambda_{max.}$(pH 1) 317 (ε 16 300), (pH 13) 336 nm (ε 16 300 dm^{-3} mol^{-1} cm^{-1}); δ[$(CD_3)_2SO$][b] 6.93 (2 H, s, NH), 7.7 (1 H, s, NH), 2.00—1.00 (8 H, m, ring CH_2), and 1.36 (3 H, s, Me).

2-*Amino*-9a,10-*dihydro*-9a-*methylcyclohexa*[g]*pteridin*-4(3H)-*one* (**14g**).—(*a*) 2-Amino-6-(1-methyl-2-oxocyclohexylamino)-5-nitropyrimidin-4(3*H*)-one (**13g**) (2.5 g) was dissolved in the minimum quantity of aqueous sodium hydroxide (2M) with heating on a steam-bath. Solid sodium dithionite was added in portions to the hot solution, further quantities of aqueous sodium hydroxide (2M) being added to keep the mixture basic, until reduction was complete as evidenced by the disappearance of the initial red colour leaving a pale yellow solution. Glacial acetic acid was added dropwise until pH 7 was reached. The mixture was then cooled and the *pteridine* (1g, 50%) was removed by filtration, m.p. >300 °C (decomp.) (Found: C, 56.6; H, 6.3; N, 29.8%; *M*, *m*/*z* 233.1284. $C_{11}H_{15}N_5O$ requires C, 56.6; H, 6.4; N, 30.05%; *M*, *m*/*z* 233.1277). $\lambda_{max.}$(pH 1) 364, 275sh, and 255 (ε 7 400, 8 300, and 22 300), (pH 13) 327, 277, and 235 nm (ε 7 600, 9 300, and 18 650 dm^{-3} mol^{-1} cm^{-1}); δ(NaOD) 2.36 (2 H, m, 6-H), 1.79 (6 H, m, 7′-, 8′-, 9′-H), and 1.29 (3 H, s, Me).

(*b*) 2-Amino-6-(2-hydroxyimino-1-methylcyclohexylamino)-5-nitropyrimidin-4(3*H*)-one (**1g**) was dissolved in the minimum quantity of aqueous sodium hydroxide (2M) and reduced as detailed above to give the pteridine (**14g**) (370 mg, 50%) identical in all respects with that obtained by method (*a*).

2-*Amino*-6-(1,1-*dimethylacetonylamino*)-5-*nitropyrimidin*-4(3H)-*one Semicarbazone* (**13h**).—(*a*) 2-Amino-6-chloro-5-nitropyrimidin-4(3*H*)-one (1.5 g, 1 equiv.) was added to 3-amino-3-methylbutan-2-one semicarbazone (1.2 g, 1 equiv.) in ethanol (20 ml) containing triethylamine (0.8 g, 1 equiv.). The resulting mixture was refluxed for 16 h and then cooled. The pyrimidine semicarbazone was filtered off and purified by dissolution in the minimum of 2M-ammonium hydroxide to yield the ammonium salt of the pyrimidine. This was dissolved in the minimum quantity of water and brought to pH 6 with dilute hydrochloric acid when the *pyrimidine semicarbazone* (1.8 g, 72%) precipitated as colourless crystals, m.p. >300 °C (Found: C, 38.1; H, 5.3; N, 35.8. $C_{10}H_{16}N_8O_4$ requires C, 38.5; H, 5.1; N, 35.9%).

(*b*) 2-Amino-6-chloro-5-nitropyrimidin-4(3*H*)-one (1.5 g, 1 equiv.), 3-amino-3-methylbutan-2-one semicarbazone hydrochloride (1.53 g, 1 equiv.) and triethylamine (1.6 g, 2 equiv.) in ethanol (25 ml) were refluxed for 16 h and then cooled. The pyrimidine semicarbazone was collected and purified as above to give colourless crystals (1.7 g, 68%) m.p. >300 °C.

2-*Amino*-6-(1,1-*dimethylacetonylamino*)-5-*nitropyrimidin*-4(3H)-*one* (**13h**; X = O).—The pyrimidine semicarbazone (1.0 g) was hydrolysed by heating it in 2M-hydrochloric acid for 30 min. The solution was cooled and brought to pH 7 with dilute ammonium hydroxide. The crude pyrimidine was collected and purified by dissolution in the minimum of dilute ammonium hydroxide and was reprecipitated with dilute hydrochloric acid as a fine white solid (0.65 g, 79%), m.p. >290 °C (Found: C, 42.3; H, 5.3; N, 27.2. $C_9H_{13}N_5O_4$ requires C, 42.35; H, 5.1; N, 27.45%).

2-*Amino*-7,8-*dihydro*-6,7,7-*trimethylpteridin*-4(3H)-*one* (**14h**).—(*a*) 2-Amino-6-(1,1-dimethylacetonylamino)-5-nitropyrimidin-4(3*H*)-one (1.0 g), was dissolved in the minimum of 2M-sodium hydroxide by heating on a steam-bath. Sodium dithionite was added portionwise until a colourless solution was obtained and this was then cooled and neutralised with acetic acid to pH 7. The dihydropteridine (0.79 g, 88%) separated and was filtered off; it was purified by dissolution in cold 0.2M-sodium hydroxide and precipitated by addition of 2M-acetic acid to pH 7. With time, the *dihydropteridine* (0.63 g, 76%) was obtained as colourless crystals, m.p. >300 °C (Found: C, 51.9; H, 6.4; N, 33.6. $C_9H_{13}N_5O$ requires C, 52.2; H, 6.3; N, 33.8%); δ(NaOD)[b] 2.05 (3 H, s, MeC=N) and 1.85 (6 H, s, Me).

(*b*) A suspension of 2-amino-6,(1,1-dimethylacetonylamino)-5-nitropyrimidin-4(3*H*)-one (1.0 g) in ethanol (30 ml) was hydrogenated over Raney nickel. When uptake of the theoretical amount of hydrogen was complete, the solution was made alkaline with 2M-sodium hydroxide, warmed, and the catalyst filtered off. The filtrate was neutralised to pH 7 with acetic acid. Refrigeration of the solution gave colourless crystals which were purified as above to give the dihydropteridine (0.39 g, 50%).

2-*Amino*-6-(1,1-*dimethyl*-2-*oxobutylamino*)-5-*nitropyrimidin*-4(3H)-*one* (**13i**).—2-Amino-2-methylpentan-3-one hydrochloride (6.08 g) was added to a suspension of 2-amino-6-chloro-5-nitropyrimidin-4(3*H*)-one (7.6 g) in ethanol (160 ml). Triethylamine (8.08 g) was added and the mixture heated to reflux; it was then refrigerated to afford the *nitropyrimidine* as a pale yellow solid. Recrystallisation from water afforded a pure specimen (3.36 g, 33%), m.p. >320 °C (Found: C, 44.3; H, 5.65; N, 25.95. $C_{10}H_{15}N_5O_4$ requires C, 44.6; H, 5.55; N, 26.05%); $\lambda_{max.}$(pH 1.2) 335 (ε 16 400), (pH 12.1) 347 nm (ε 20 000 dm^{-3} mol^{-1} cm^{-1}); δ(NaOD)[b] 1.47 (6 H, s, Me) and 0.99 (3 H, t, CH_2Me).

2-*Amino*-6-*ethyl*-7,8-*dihydro*-7,7-*dimethylpteridin*-4(3H)-*one* (**14i**).—2-Amino-4-(1,1-dimethyl-2-oxobutylamino)-6-hydroxy-5-nitropyrimidine (3.3 g) was dissolved in the minimum of 2M-sodium hydroxide solution at 60 °C and treated with solid sodium dithionite, added portionwise with swirling, until the amber solution changed through deep red to give a pale yellow solution. The pH of the solution was adjusted to 8 by the addition of a little dilute acetic acid and the mixture allowed to cool whereupon the crude product separated as a colourless microcrystalline solid. Purification was achieved by dissolution of the crude product in 1M-sodium hydroxide solution, filtration of the solution and addition of glacial acetic acid to pH 8.0 to precipitate the required pteridine (1.16 g, 43%), m.p. 280—284 °C (Found: C, 54.0; H, 6.95; N, 32.05. $C_{10}H_{15}N_5O$ requires C, 54.25; H, 6.75; N, 31.75%); $\lambda_{max.}$(pH 1.4) 358, 275sh, and 255 nm (ε 6 700, 8 400, and 15 000), (pH 12.1) 319 and 283 nm (ε 6 800 and 8 200 dm^{-3} mol^{-1} cm^{-1}); δ(NaOD)[b] 2.36 (2 H, q, CH_2Me), 1.26 (6 H, s, Me), and 1.12 (3 H, t, CH_2Me).

2-*Amino*-6-(1,1-*dimethyl*-2-*oxopentylamino*)-5-*nitropyrimidin*-4(3H)-*one* (**13j**).—2-Amino-2-methylhexan-3-one hydrochloride (8.25 g) was added to a suspension of 2-amino-6-chloro-5-nitropyrimidin-4(3*H*)-one (9.5 g) in ethanol (200 ml). Triethylamine (10.1 g) was added and the mixture was refluxed for 24 h after which time it was diluted with water (250 ml), heated to reflux, and filtered whilst hot. Refrigeration of the filtrate gave the crude product which on recrystallisation from water afforded the *nitropyrimidine* as a pale yellow microcrystalline solid (6.92 g, 55%), m.p. 280 °C (Found: C, 43.6; H, 6.2; N, 23.0. $C_{11}H_{17}N_5O_4 \cdot H_2O$ requires C, 43.85; H, 6.35; N, 23.25%); $\lambda_{max.}$(pH 1) 334 and (pH 13) 347 nm.

2-*Amino*-6-*propyl*-7,7-*dimethyl*-7,8-*dihydropteridin*-4(3H)-*one* (**14j**).—2-Amino-6-(1,1-dimethyl-2-oxopentylamino)-5-nitropyrimidin-4(3*H*)-one (6.0 g) was dissolved in 1M-sodium hydroxide (40 ml) with heating on a steam-bath. Solid sodium *dithionite* was added portionwise with stirring until the colour changed from amber to deep red to pale yellow. Cooling gave the crude product as a whitish green solid. Purification by dissolution in 2M-sodium hydroxide and filtration followed by addition of glacial acetic acid to pH 8 gave the *pteridine* as an off-white solid (4.57 g, 91%), m.p. 300 °C (Found: C, 56.1; H, 7.5; N, 29.5. $C_{11}H_{17}N_5O$ requires C, 56.2; H, 7.24; N, 29.8%); $\lambda_{max.}$(pH 1) 353, 270sh, and 254 (ε 9 300, 7 600, and 21 000), (pH 13) 318 and 281 nm (ε 9 150 and 10 700 dm^3 mol^{-1} cm^{-1}).

2-*Amino*-7,8,8a,9-*tetrahydro*-8a-*methyl*-6H-*cyclopenta*[g]-*pteridine*-4,6(3H,7H)-*dione* (**14k**).—2-Amino-8a,9-dihydro-8a-methylcyclopenta[*g*]pteridine-4(3*H*)-one dihydrogen sulphite (**14f**) (500 mg) was dissolved in a mixture of butan-1-ol (12.5 ml), glacial acetic acid (5 mol), and water (7.5 ml) with warming. This mixture was then stirred overnight at room temperature and applied to a column of CG-50 ion exchange resin (15 cm × 2.5 cm) eluting with 20% methanol–water. The fractions containing the product were evaporated under reduced pressure to low volume (*ca.* 3 ml) and allowed to stand overnight at 0 °C. The *pteridinedione* (137 mg, 38%) was collected as dark brown crystals on filtration, m.p. >300 °C (decomp.) (Found: C, 51.3; H, 4.8; N, 29.8%; *M*, *m/z* 233.0902. $C_{10}H_{11}N_5O_2$ requires C, 51.5; H, 4.7; N, 30.05%; *M*, *m/z* 233.0913); $\lambda_{max.}$(pH 1.3) 422 and 273 (ε 6 020 and 6 680), (pH 12.9) 462, 352, and 271 nm (ε 5 230, 9 950, and 9 400 dm^3 mol^{-1} cm^{-1}).

2-*Amino*-8,9,9a,10-*tetrahydro*-9a-*methylcyclohexa*[g]-*pteridine*-4,6(3H,7H)-*dione* (**14l**).—2-Amino-8,9,9a,10-tetrahydro-9a-methylcyclohexa[*g*]pteridin-4(3*H*)-one (**14g**) (1.8 g) was dissolved in a mixture of butan-1-ol (25 ml), glacial acetic acid (10 ml), and water (15 ml). After the mixture had been stirred overnight with free access of air the volatile material was removed under reduced pressure and the residue dissolved in the minimum quantity of 50% aqueous methanol. This solution was applied to a column of CG-50 ion exchange resin (H^+ form) (30 cm × 2.5 cm) and eluted with 20% methanol–water. The fractions containing the product were collected and the solvent removed under reduced pressure to give the *pteridinedione* (1.22 g, 74%) as an orange powder, m.p. >250 °C (decomp.) A satisfactory N analysis could not be obtained (Found: C, 51.3; H, 5.3; N, 26.5%; *M*, *m/z* 247.1069. $C_{11}H_{13}N_5O_2 \cdot \frac{1}{2}H_2O$ requires, C, 51.55; H, 5.45; N, 27.3%. *M*, *m/z* 247.1069); $\lambda_{max.}$(pH 1.2) 412 and 271 (ε 13 400 and 15 100), (pH 12.3) 444 and 267 nm (ε 15 300 and 17 500 dm^3 mol^{-1} cm^{-1}); δ[$(CD_3)_2SO$][b] 7.80 (1 H, s, NH), 7.20 (1 H, s, NH), 6.63 (2 H, s, NH_2), 3.40 (2 H, m, 7′-H), 1.93 (4 H, m, 8′-, 9′H), and 1.07 (3 H, s, Me).

6-*Acetyl*-2-*amino*-7,8-*dihydro*-7,7-*dimethylpteridin*-4(3H)-*one* (**14m**).—The above 6-ethylpteridine (**14i**) (2 g) and butanol–acetic acid–water (5:2:3) (50 ml) were placed in a flask completely covered in aluminium foil in order to protect the contents from light. The mixture was then allowed free access of air whilst it was vigorously stirred for 6 h at 60 °C. The resulting mixture was then applied to a column of CG-50 ion exchange resin (30 cm × 2.5 cm) (H^+ form) and eluted with 20% aqueous propan-2-ol. That portion of the eluate containing the product was evaporated to low volume (*ca.* 10 ml) and allowed to stand overnight at 0 °C. The resulting orange needles of the 6-*acetylpteridine* (1.8 g, 83%) were removed by filtration, m.p. >250 °C (decomp.) (Found: C, 49.7; H, 5.5; N, 29.4%; *M*, *m/z* 235.1072. $C_{10}H_{13}N_5O_2 \cdot 0.25H_2O$ requires C, 50.05; H, 5.65; N, 29.35%; *M*, *m/z* 235.1069); $\lambda_{max.}$(pH 1.3) 398, 280sh, and 266 (ε 8 100, 9 400, and 11 900), (pH 12.1) 424 and 266 nm (ε 11 400 and 16 200); δ[$(CD_3)_2SO$][b] 7.30 (1 H, s, NH), 6.52 (2 H, s, NH_2), 6.00 (1 H, s, NH), 2.22 (3 H, s, MeCO), and 1.38 (6 H, s, Me).

2-*Amino*-6-*formyl*-7,8-*dihydro*-7,7-*dimethylpteridin*-4(3H)-*one* (**14n**).—A 2:1.5 mixture of sulphur dioxide and oxygen was passed through a stirred suspension of 2-amino-7,8-dihydro-6-hydroxymethyl-7,7-dimethylpteridin-4(3*H*)-one (0.8 g) in saturated aqueous sulphurous acid (15 ml) for 9 h. The resulting colourless suspension was stored for 12 h at 4 °C, saturated with sulphur dioxide and filtered. The solid which was obtained was washed with ice-cold aqueous sulphurous acid (5 ml) to give the bisulphite adduct. The required formylpteridine was isolated by suspending the adduct in water (15 ml), heating the mixture to 70 °C and treating it with a current of nitrogen until evolution of sulphur dioxide was complete (30 min). The suspension was cooled and the solid was removed by filtration, washed with water (10 ml) and ethanol (10 ml), and dried to give the formylpteridine as a green powder (0.5 g, 63%); $\lambda_{max.}$(pH 1) 400 and 279sh, (pH 13) 432 and 265 nm; δ(CF_3CO_2H)[a] 10.4 (1 H, s, CHO) and 1.8 (6 H, s, Me).

2-*Amino*-6-*formyl*-7,8-*dihydro*-7-*methyl*-7-*phenethylpteridin*-4(3H)-*one* (**14o**).—A suspension of the foregoing pteridine (**14c**) (200 mg) in butanol–acetic acid–water (5:2:3) was stirred overnight in the presence of air. The mixture was evaporated to a semi-solid gum which was dissolved in a small volume of ethanol and applied to a column (2 × 30 cm) of CG-50 ion exchange resin. The column was washed well with water, and the product eluted as a yellow band with ethanol. This fraction was evaporated to a low volume and the resulting solid collected by filtration. The product (160 mg, 80%) was further purified by dissolution in 80% ethanol, evaporation to a low volume, and collection of the resulting crystals by filtration to give the 6-*formylpteridine* as yellow plates, m.p. 280 °C (decomp.) (Found: C, 61.5; H, 5.4; N, 22.5. $C_{16}H_{17}N_5O_2$ requires C, 61.7, H, 5.5; N, 22.5%); $\lambda_{max.}$(pH 1) 413 and 269 (ε 4 230 and 6 060), (pH 14) 442 and 267 nm (ε 14 200 and 18 500 dm^3 mol^{-1} cm^{-1}); δ[$(CD_3)_2SO$][b] 0.09 (1 H, s, CHO), 7.68 (1 H, s, NH), 7.04 (5 H, s, Ar), 2.60—1.60 (4 H, m, CH_2CH_2Ph), and 1.40 (3 H, s, Me).

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