328. *Pteridine Studies. Part XXV.*[1] *Preparation, Hydration, and Degradation of some Chloropteridines.*

By Adrien Albert and Jim Clark.

Improved methods have been found for the preparation of 6- and 7-chloropteridine. 6,7-Dichloropteridine is described for the first time.

In aqueous solution, each of these compounds is, in part, reversibly covalently hydrated at the 3,4-double bond; some first-order rate constants for the hydration and dehydration reactions have been determined.

The chloropteridines have been degraded, under acid conditions, to chloropyrazine derivatives.

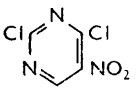
It has generally been assumed that the dominating feature of the chemistry of 6- and 7-chloropteridine is the ease of replacement of the reactive chlorine atom by a nucleophilic reagent. It has now been found that, in these compounds, there are two sites which are readily attacked by nucleophiles, namely the chlorine atom and the 3,4-double bond. This discovery has led to a better understanding of the reactions of these substances and to improved methods of preparation.

[1] Part XXIV, Albert, Inoue, and Perrin, *J.*, 1963, 5151.

Published methods for the synthesis of 6- and 7-chloropteridine [2,3] give erratic results, and yields fall rapidly if experiments are attempted on a scale larger than about 1 gram. The lack of practical routes to these compounds has greatly hindered the study of pteridines substituted only in the pyrazine ring. In a new approach hydroxypteridines have been treated with phosphorus pentachloride in special solvents, and the chloro-compounds isolated under non-aqueous conditions. This avoids hitherto unsuspected hydrolysis, hydration, and ring-opening reactions, which occur in aqueous solution and which are described in detail below.

A 90% yield of 7-chloropteridine was obtained by treating a solution of the hydroxy-compound in boiling pentachloroethane (b. p. 162°) with phosphorus pentachloride, and the yield was maintained on the largest scale attempted (6 grams). The solvent itself reacted slowly with the phosphorus halide; this ensured that no reagent was left at the end of the reaction and made working-up very simple. When the mixture was heated slowly to 160°, early precipitation of 7-hydroxypteridine hydrochloride prevented the desired reaction from taking place, and the reagent then attacked the solvent almost exclusively.

Because 6-hydroxypteridine (known only as its monohydrate) is nearly insoluble in pentachloroethane, this solvent could not be used in the preparation of 6-chloropteridine. However, phosphoryl chloride was satisfactory as solvent, in conjunction with two molecular proportions of phosphorus pentachloride, one of which was required to take up the molecule of water from the hydrated starting material and the other to effect the chlorination. Under these conditions, little phosphorus pentachloride was left at the end of the reaction and 55—66% of 6-chloropteridine was obtained.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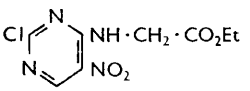
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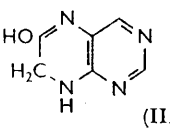

(III)

A shorter route to 6-chloropteridine was found by way of 7,8-dihydro-6-hydroxypteridine (III), which was simultaneously oxidised and converted into the chloro-compound (36% yield) by a mixture of phosphoryl chloride and phosphorus pentachloride. The dihydro-derivative (III) was made by condensing 2,4-dichloro-5-nitropyrimidine (I) with ethyl aminoacetate, to give a product (II) which was reduced, cyclised, and dehalogenated all in one step, thus greatly simplifying the method described by Boon, Jones, and Ramage.[4]

There was no apparent reaction between phosphorus pentachloride and 6,7-dihydroxy-pteridine in boiling phosphoryl chloride or pentachlorethane, but it was gradually converted into 6,7-dichloropteridine by treatment with phosphorus pentachloride in benzoyl chloride at 140°. If a larger quantity of phosphorus pentachloride, a higher reaction temperature, or an unduly extended reaction time was used, the yield was lowered by ring-opening reactions which led to pyrazine derivatives. There was no evidence of benzoylation, although α- and γ-hydroxy-N-heterocycles had occasionally been acylated on nitrogen [5] and possibly on oxygen.[6]

The chloropteridines were not found as salts or complexes at the end of the above reactions. This indicates that they are very weak bases in the anhydrous state, and suggests that they, like pteridine and the methylpteridines, owe their basic properties in aqueous solution (Table 1) to partial hydration.[7,8] Hydration is meant to imply addition

[2] Albert, Brown, and Cheeseman, *J.*, 1952, 1620.
[3] Albert, Brown, and Wood, *J.*, 1954, 3832.
[4] Boon, Jones, and Ramage, *J.*, 1951, 96.
[5] Spector and Keller, *J. Biol. Chem.*, 1958, **232**, 185; Bredereck, Gompper, and Herlinger, *Chem. Ber.*, 1958, **91**, 2832.
[6] Ellinger and Riesser, *Ber.*, 1909, **42**, 3336; Schaaf and Spoerri, *J. Amer. Chem. Soc.*, 1949, **71**, 2043.
[7] Perrin, *J.*, 1962, 645.
[8] Inoue and Perrin, *J.*, 1963, 2648.

of a molecule of water across a C=N linkage, as in (IV ⟶ V) for example; factors which favour such additions have been discussed.[9]

The pK_a value for the anhydrous species of pteridine is probably close to −2. This figure is estimated from the pK_a of isoquinoline, 5·4, by making allowance for the base-weakening effect, in pteridine, of N-1, N-5, and N-8 on the N-3 atom, which is almost certainly the site of protonation. The effects of N-5 and N-8 were taken as 1·6 and 1·8 units, respectively, from comparison of isoquinoline with 1,6- and 1,7-naphthyridine,[10] and the effect of N-1 was taken as 3·9 units from comparison of pyridine and pyrimidine (quinazoline cannot be used as a reference compound because it, too, is partly hydrated in aqueous solution [11]). The chloropteridines are presumably still more weakly basic than pteridine.

TABLE 1.

pK_a Values and absorption spectra of some chloropteridines and chloropyrazines.

Compound	pK_a	Species [b]	$\lambda_{max.}$ (mμ) [c]	log ε [c]	pH
		Pteridine			
6-Chloro	3·72 ± 0·05 [d]	AO	213, *236*, *298*, 309, 322 [e]	4·23, *3·71*, *3·77*, 3·94, 3·91	6·9
		HO	236, 277, 330	3·74, 3·88, 3·93	6·9
		HZ	261, 311 [f]	3·77, 4·01	1·0
7-Chloro	3·26 ± 0·03 [d]	AO	*281*, *285*, *292*, *297*, 304, 309, 317 [e]	*3·60*, *3·70*, *3·86*, *3·93*, 4·04, 4·00, 4·05	7·0
		HO	238, 276, 327	3·62, 3·64, 4·02	6·4
		HZ	255, 310	3·56, 4·06	1·1
6,7-Dichloro	3·27 ± 0·04 [d]	AO	225, *302*, 315, 328 [e]	4·09, *3·80*, 4·02, 4·01	7·0
		HO	243, 281, 337	3·69, 3·82, 4·02	7·0
		HZ	264, 319	3·70, 4·10	1·1
		Pyrazine			
5-Chloro-2-formamido-3-formyl	—	O	245, 272, 316	4·00, 3·89, 3·73	7·0
2-Amino-5-chloro-3-formyl	−0·68 ± 0·03	O	*217*, 270, 388	*3·83*, 3·96, 3·80	7·0
		Z	*248*, 263, 386 [e]	*3·80*, 3·89, 3·73	−2·8 [g]
6-Chloro-2-formamido-3-formyl	—	O	211, 227, 273, 318	4·12, 4·01, 4·01, 3·92	7·0
2-Amino-6-chloro-3-formyl	−1·64 ± 0·03	O	211, 232, 268, 372	3·98, 3·90, 3·90, 3·97	7·0
		Z	253, *267*, 374	3·89, *3·81*, 3·77	−3·6 [g]
5,6-Dichloro-2-formamido-3-formyl	—	O	209, 245, 277, 325	4·02, 4·01, 3·93, 3·87	7·0
2-Amino-5,6-dichloro-3-formyl	—	O	223, 273, 388	3·95, 4·00, 3·93	7·0

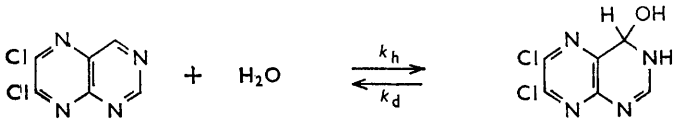
[a] Determined spectroscopically at 20°. [b] O = neutral species, Z = cation, A = anhydrous, H = hydrated. [c] In water; shoulders and inflexions in italics. [d] Equilibrium pK_a. [e] By extrapolation back to time of dissolution. [f] By continuous-flow method. [g] H_0 (sulphuric acid) (from Paul and Long, *Chem. Rev.*, 1957, **57**, 12).

6- and 7-Chloropteridine are unstable in aqueous solution, and it was assumed [2,12] that hydrolysis of the chlorine atom was occurring. It is now shown that this is not always the only, or even the major, reaction in aqueous solution.

The spectral changes which occur when 6-, 7-, or 6,7-dichloropteridine is dissolved in neutral aqueous solution very closely resemble those observed when pteridine is similarly treated.[7] In all cases, partial reversible covalent hydration at the 3,4-double bond (*e.g.*, IV ⟶ V) is the first reaction observed, and this is followed by slower, ring-opening reactions which are described below. In neutral or weakly acidic solutions, hydrolysis of a chlorine atom appeared to be negligible in the case of 7- and 6,7-dichloropteridine, but it may be more important in the 6-isomer. The cations of all the compounds appeared to be almost completely hydrated.

[9] Albert and Barlin, *J.*, 1963, 5156.
[10] Albert, *J.*, 1960, 1790.
[11] Albert, Armarego, and Spinner, *J.*, 1961, 2689.
[12] Albert, *Quart. Rev.*, 1952, **6**, 220.

The first-order rate constants for hydration (k_h) and dehydration (k_d) have been determined for each chloro-compound under one set of conditions, and these are compared with those for pteridine (Table 2). The constants were measured by a spectrophotometric method essentially as described previously,[8] but modified to allow for side-reactions which,



(IV) (V)

particularly in 6- and 6,7-dichloropteridine, prevented the main reaction from being accurately followed to completion. This difficulty was minimised by following the changes towards equilibrium from the anhydrous state, as well as from the fully hydrated state. Optical density measurements at a particular wavelength were made as before, but only during the early stages of each experiment, when the effect of side-reactions was least important. The approximate optical density at equilibrium was obtained, by extrapolation, from both forward and back reactions, and the precise value (D_{eq}) fixed by applying the criteria: (i) D_{eq} is to be the same for forward and back reactions; and (ii) k_{obs} is to be the same for forward and back reactions ($k_{obs} = k_h + k_d$).[8] The individual rate constants k_h and k_d follow from $k_h/k_d = [A_{eq}]/[P_{eq}]$ where $[P_{eq}]$ and $[A_{eq}]$ are the concentrations of anhydrous and hydrated species, respectively, at equilibrium. In the pH range used, the concentrations of cations are negligible.

TABLE 2.

Equilibria and first-order rate constants (sec.$^{-1}$) for hydration and dehydration at 20°.

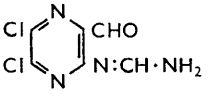
Compound	pH	$\lambda_{max.}$ (mμ) for measurements	10^4k_{obs}	10^4k_h	10^4k_d	$[A_{eq}]/[P_{eq}]$	True pK_a of hydrate
Pteridine [8]	7·17		2·88	0·646	2·23	1 : 3·5	4·79
	6·75		4·41	0·989	3·42		
6-Chloropteridine ...	6·89	309	3·88	1·23	2·65	1 : 2·2	4·22
7-Chloropteridine.....	6·80	304	5·20	1·55	3·65	1 : 2·35	3·79
6,7-Dichloropteridine	7·00	315	3·10	1·10	2·00	1 : 1·8	3·72

$[A_{eq}]/[P_{eq}]$ is the ratio of the concentrations of hydrated and anhydrous species at equilibrium. True pK_a values refer to cations of hydrated species; equilibrium pK_a values are given in Table 1.

The results (Table 2) show that the chloropteridines are all more hydrated at equilibrium than pteridine. This is attributed to the inductive effect of the chlorine atoms, which reduces the electron density at position 4 and increases polarisation of the 3,4-bond. However, comparison of the rate constants for hydration and dehydration of chloropteridines with those for pteridine show that the chlorine atoms have only a small effect on the rate of the reactions. pK_a values for the hydrated chloropteridines were obtained from measured equilibrium pK_a values by correcting for the anhydrous species present,[7] and the values show the expected small base-weakening effect of chlorine atoms at some distance from the site of protonation.

Degradation of Chloropteridines.—The degradation of chloropteridines is of interest in connection with the dual reactivity of these compounds and also as a route to potentially useful pyrazine derivatives. The chloropteridines were unstable in aqueous solution under all conditions, but the nature of the products varied with pH, temperature, concentration, and the nature of the acid or base. In cold sodium carbonate solution, 6- and 7-chloropteridine were rapidly converted into the corresponding hydroxypteridines, and 6,7-dichloropteridine yielded 6-chloro-7-hydroxypteridine. However, in mildly acidic solutions nucleophilic attack favoured the 4-position, so that 6,7-dichloropteridine, for example, yielded (in turn) the sulphate of hydrated 6,7-dichloropteridine (V), the formamidopyrazine

aldehyde (VII), and the aminopyrazine aldehyde (VIII). By careful control of conditions any one of these could be obtained in high yield. The amidine (VI), which is presumably the first ring-opened product, appeared to be unstable to acid, and the reaction could not be stopped at this stage.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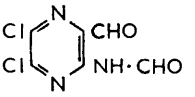
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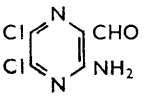
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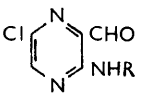
(IX)

Hydrated 6,7-dichloropteridine (V) and the amidine (VI) have the same molecular formula, and analytical figures for the product obtained under very mild conditions would fit either of these compounds (as sulphate). The following facts show that the product was the hydrated pteridine derivative. The ultraviolet spectrum of the substance in 0·1N-hydrochloric acid was identical with that of 6,7-dichloropteridine. The spectrum of the substance immediately after dissolution (<1 minute) in pH 7 buffer was identical with that of hydrated neutral 6,7-dichloropteridine, and the spectrum gradually changed to that of the equilibrium mixture of hydrated and anhydrous forms. The infrared spectrum (KBr disc) of the compound had only one absorption band (at 1670 cm.$^{-1}$) in the 1630—1750 cm.$^{-1}$ region, and this was attributed to the amidinium system; there was no carbonyl stretching band.

7-Chloropteridine gave analogous degradation products in good yield. It was much more difficult to separate the hydrolysis and ring-opening reactions with 6-chloropteridine, which was completely converted into 6-hydroxypteridine by cold N-hydrochloric acid as well as by cold sodium carbonate. A modest yield of the formamidoderivative (IX; R = CHO) was obtained by degradation in pH 4 buffer, and a similar yield of the aminopyrazine aldehyde (IX; R = H) resulted from degradation in pH 3·3 buffer. Ring-opening of pteridine derivatives is known to occur in acid conditions by an uncatalysed decomposition of the cation, and also by an acid-catalysed reaction.[8] It will be noted that 6-chloropteridine yielded pyrazine derivatives when the pH of the solution was close to its equilibrium pK_a value, *i.e.*, when the concentration of cation was high but the concentrations of hydroxyl and hydronium ions were low, and hence chlorine hydrolysis was slow.

Cation formation usually increases the reactivity of chlorine atoms in nitrogen heterocycles [13] but 7- and 6,7-dichloropteridine were fairly stable at pH 0. This is apparently due to the fact that the cations are virtually completely hydrated, and the chlorine atoms in the hydrated species (even cations) seem to resemble those of pyrazine derivatives, which are only feebly reactive,[14] rather than those of fully aromatic pteridines. Pteridine itself yields pyrazine derivatives under both acid and alkaline conditions.[15]

Formamidopyrazine aldehydes (*e.g.*, VII) were readily deformylated under acid or alkaline conditions. The chlorine atoms in the aminopyrazine aldehydes produced (*e.g.*, VIII) were much more stable to alkali than those of the parent pteridines. The aminoaldehydes are very weak bases (Table 1) which form cations bearing a proton at N-1. Protonation clearly does not take place on the exocyclic nitrogen atom because it has practically no effect on the longest wavelength ultraviolet absorption band.[16] Moreover, 2-amino-3-formyl-6-chloropyrazine is a much weaker base than its 5-chloro-isomer (IX; R = H), showing that the 6-chlorine atom is adjacent to the basic centre. Protonation at N-1 is presumably favoured by the 2-aminopyridinium-type resonance which becomes possible in the cation.[17]

[13] Banks, *J. Amer. Chem. Soc.*, 1944, **66**, 1127.
[14] Baxter and Spring, *J.*, 1947, 1179.
[15] Albert, Brown, and Wood, *J.*, 1956, 2066.
[16] Craig and Short, *J.*, 1945, 419.
[17] Albert, Goldacre, and Phillips, *J.*, 1948, 2240.

Experimental

Microanalyses were by Dr. J. E. Fildes and her staff. The spectra of species which were stable under the conditions of measurement were measured first on a Perkin-Elmer Spectrocord recording spectrophotometer and then the $\lambda_{max.}$ and $\varepsilon_{max.}$ values were checked on a Hilger Uvispek manual instrument (by Mr C. Arandjelovic). The spectra of less-stable species were determined on a Shimadzu Model RS27 recording spectrophotometer. In some cases a rapid reaction apparatus [18] was used, and in others spectral changes were followed for a short time and extrapolated back to the time of dissolution.

Kinetic Measurements.—Each hydration–dehydration reaction was studied spectrophotometrically from the fully hydrated side by mixing an acidified solution (pH 1·1) of the pteridine with buffer solution and alkali, in a rapid-reaction apparatus as described by Inoue and Perrin.[8] The reaction was followed from the anhydrous side by quickly dissolving the anhydrous solid pteridine in buffer solution containing sodium chloride, and again following changes spectrophotometrically. The spectrum of the fully anhydrous species was obtained by extrapolation back to the time of dissolution. The final pH, ionic strength, and pteridine concentration were the same in each case. The measurements were made at a wavelength (Table 2) where the spectral effect of a small amount of ring-opening would be minimised. Only readings obtained during about the first 15 min. of each reaction were used in determining the rate constants.

7-Chloropteridine.—7-Hydroxypteridine (6 g.) was dissolved in boiling pentachloroethane (500 ml.), and 200 ml. of the solvent was distilled off. Heating was discontinued, and phosphorus pentachloride (12·4 g.) was added immediately (vigorous reaction). The mixture was heated under reflux for 10 min., and volatile constituents removed at 45°/0·5 mm. in a rotary evaporator set so that the mouth of the distillation flask sloped slightly downwards. The residue was extracted several times with cold benzene (total 250 ml.), and the combined, filtered extracts were evaporated at 30°, to yield 7-chloropteridine (6·06 g.), m. p. 99—100°. A pure specimen, prepared by sublimation at 80°/0·5 mm., or crystallisation from light petroleum (b. p. 60—80°), had m. p. 100—101° (lit.,[3] 95°).

6-Chloropteridine.—(*a*) Phosphoryl chloride (75 ml.) and phosphorus pentachloride (6·5 g.) were heated to 100°, and finely ground 6-hydroxypteridine hydrate (2·5 g.) was added. The mixture was stirred at 125° (bath) for 1 hr., before the solvent was removed under reduced pressure at 95° (air excluded *). The residue was thoroughly dried for a further ½ hr. at 95°/10 mm., and then extracted twice with boiling light petroleum (b. p. 60—80°) (total 320 ml.) to yield 55—66% of 6-chloropteridine (2 crops). The m. p., 148—150°, was raised to 149—150° (lit.,[2] 146—147°) by recrystallisation from the same solvent.

(*b*) 7,8-Dihydro-6-hydroxypteridine (2·5 g.) was treated as described in (*a*) above, to yield 6-chloropteridine (36%). Water (30 ml.) and an excess of hydrochloric acid were added to the petroleum-insoluble residue, and insoluble matter was filtered off. Addition of an excess of 5N-sodium hydroxide to the filtrate gave the sodium salt of 7,8-dihydro-6-hydroxypteridine (35%).

Ethyl N-(2-chloro-5-nitropyrimidin-4-yl)aminoacetate (II).—Ethyl aminoacetate hydrochloride (16 g.) was added, with stirring, to a mixture of 2,4-dichloro-5-nitropyrimidine (15·6 g.), in chloroform (120 ml.), and saturated sodium hydrogen carbonate solution (200 ml.). After being stirred for a further ½ hr., the chloroform layer was separated, washed with water, dried, and evaporated. The residue was crystallised from light petroleum (b. p. 60—80°; 120 ml.), containing just sufficient ethyl acetate to give a clear solution at the boil, to give the aminoacetate (80%; 2 crops) as pale yellow needles, m. p. 102—105° (lit.,[4] 101—102°).

7,8-Dihydro-6-hydroxypteridine (III).—Ethyl *N*-(2-chloro-5-nitropyrimidin-4-yl)aminoacetate (8·23 g.) and hydriodic acid (*d* 1·94; 36 ml.) were swirled gently (500 ml. flask) for ½ min., and red phosphorus (4·11 g.) was added (vigorous reaction). The mixture was heated under reflux for ½ hr., cooled, and filtered through sintered glass. The solution was made strongly alkaline with 5N-sodium hydroxide, cooled, and filtered. The sodium salt was dissolved in 2N-hydrochloric acid (charcoal), and 7,8-dihydro-6-hydroxypteridine (77%) was precipitated by the addition of an excess of sodium acetate (Found: C, 48·05; H, 4·1. Calc. for $C_6H_6N_4O$: C, 48·0; H, 4·0%).

* If air was admitted at this point a red hydrochloride was formed, and this yielded a purple base, apparently a dimer or polymer of 6-chloropteridine.

[18] Inoue and Perrin, *J. Phys. Chem.*, 1962, **66**, 1689.

6,7-*Dichloropteridine*.—Finely ground 6,7-dihydroxypteridine (3·28 g.; previously dried at 120°), phosphorus pentachloride (10 g.), and benzoyl chloride (80 ml.) were rapidly heated to 140° (bath), and stirred at that temperature for 6 hr. The solvent was rapidly and completely removed at 65°/0·5 mm., using a rotary evaporator set so that the neck of the distillation flask sloped slightly downwards. The residue was extracted twice with boiling light petroleum (b. p. 60—80°; total 500 ml.), and the combined extracts yielded crude 6,7-*dichloropteridine* (2 crops; 2·52 g.), m. p. 130—135°, suitable for preparative purposes. A pure specimen, m. p. 141—142°, was prepared by sublimation at 85°/0·5 mm. followed by crystallisation from light petroleum (b. p. 60—80°) (Found: C, 35·5; H, 1·1; N, 27·8. $C_6H_2Cl_2N_4$ requires C, 35·85; H, 1·0; N, 27·9%).

Degradation of 7-*Chloropteridine*.—(*a*) 7-Chloropteridine (0·167 g.) and 0·1N-hydrochloric acid (5 ml.) were heated on a steam-bath for 10 min. The flask was swirled and its surface scratched with a glass rod to induce crystallisation as soon as possible after the reaction started (*ca.* 3 min.). The mixture was cooled, and a pale yellow solid (0·140 g.) filtered off. This solid was separated, by repeated fractional sublimation at 0·5 mm. within the range 40—80°, into colourless 6-*chloro*-2-*formamido*-3-*formylpyrazine* (0·11 g., 66%), m. p. 140—141°, and a yellow amino-aldehyde, m. p. 151—152° (0·01 g.), obtained in higher yield in (*b*). The formamido-derivative was finally recrystallised from light petroleum (b. p. 60—80°) (Found: C, 39·0; H, 2·1; Cl, 19·15; N, 22·35. $C_6H_4ClN_3O_2$ requires C, 38·8; H, 2·2; Cl, 19·1; N, 22·6%).

(*b*) 7-Chloropteridine (0·167 g.) and 0·1N-sulphuric acid (10 ml.) were stirred, on a steam-bath, for 10 min., cooled, and filtered. The pale yellow solid, which contained the two compounds mentioned in (*a*) above, was shaken with cold 2N-sodium carbonate solution (5 ml.) for 5 min.; 2-*amino*-6-*chloro*-3-*formylpyrazine* (0·115 g., 73%) was filtered off, and it crystallised from light petroleum (b. p. 60—80°) as a yellow solid, m. p. 151—152° (Found: C, 38·4; H, 2·6; N, 26·3. $C_5H_4ClN_3O$ requires C, 38·1; H, 2·6; N, 26·7%).

(*c*) A mixture of 7-chloropteridine (0·084 g.) and N-sodium carbonate solution (2·5 ml.) was shaken for 15 min. at 20°. The sodium salt of 7-hydroxypteridine (86%) was filtered off, and its structure confirmed by infrared spectroscopy.

Degradation of 6,7-*Dichloropteridine*.—(*a*) 6,7-Dichloropteridine (0·2 g.) and 0·25N-sulphuric acid (5 ml.) were stirred at 65° (bath) for 8 min., and the mixture was cooled and filtered. The pale yellow solid (0·23 g.) was extracted several times with boiling light petroleum (b. p. 60—80°), leaving 6,7-*dichloro*-3,4-*dihydro*-4-*hydroxypteridine sulphate* which gradually decomposed above 160° (Found: C, 27·3; H, 2·0; N, 20·8. $C_6H_4Cl_2N_4O,\frac{1}{2}H_2SO_4$ requires C, 26·9; H, 1·9; N, 20·9%).

(*b*) A mixture of 6,7-dichloropteridine (0·2 g.) and 0·1N-hydrochloric acid (5 ml.) was stirred on the steam-bath for 5 min., thoroughly cooled, and filtered. The residue (0·160 g.), m. p. 138—145°, was shown by infrared spectroscopy to be almost all 5,6-*dichloro*-2-*formamido*-3-*formylpyrazine* (VII). The crude material was sublimed at 90°/1 mm. (after rejecting a few mg. which sublimed at 60°/1 mm.), to yield 62% of fairly pure material which was crystallised from light petroleum (b. p. 60—80°) as a nearly colourless solid, m. p. 153—154° (Found: C, 33·0; H, 1·3; N, 19·4. $C_6H_3Cl_2N_3O_2$ requires C, 32·75; H, 1·4; N, 19·1%).

(*c*) A mixture of 6,7-dichloropteridine (0·2 g.) and 0·1N-sulphuric acid (15 ml.) was stirred on a steam-bath for ½ hr., cooled, and filtered. The dried residue (0·14 g.) crystallised from light petroleum (b. p. 60—80°) as yellow 2-*amino*-5,6-*dichloro*-3-*formylpyrazine* (VIII) (2 crops; 67%), m. p. 154° (Found: C, 31·45; H, 1·75; Cl, 37·4; N, 21·9. $C_5H_3Cl_2N_3O$ requires C, 31·3; H, 1·6; Cl, 36·9; N, 21·9%).

Degradation of 6-*Chloropteridine*.—(*a*) A mixture of 6-chloropteridine (0·3 g.) and 0·5M-acetate buffer (60 ml.; pH 4) was stirred at 75° for ½ hr., and evaporated at 30°. The residue was dried in a desiccator ($CaCl_2$ and KOH) and sublimed. A small fraction, b. p. 60°/0·5 mm., was rejected, and the main fraction, b. p. 100°/0·5 mm., was 5-*chloro*-2-*formamido*-3-*formylpyrazine* (0·06 g., 18%), which crystallised from light petroleum (b. p. 60—80°) as a white solid, m. p. 163° (Found: C, 39·0; H, 2·2; N, 22·6. $C_6H_4ClN_3O_2$ requires C, 38·8; H, 2·2; N, 22·6%).

(*b*) A mixture of 6-chloropteridine (0·5 g.) and 0·5M-acetate buffer (50 ml.; pH 3·3) was stirred, under nitrogen, at 75° for 4 hr. The solution was cooled, adjusted to pH 7 (5N-sodium hydroxide), and evaporated to dryness at 30°. Benzene and ethanol, and finally benzene alone, were evaporated from the residue under reduced pressure, and the material was dried in a vacuum desiccator. Sublimation at 60°/0·5 mm. yielded 2-*amino*-5-*chloro*-3-*formylpyrazine* (0·082 g.), m. p. 158—159°, which crystallised from light petroleum (b. p. 60—80°) as bright

yellow prisms (Found: C, 38·2; H, 2·5; N, 26·4. $C_5H_4ClN_3O$ requires C, 38·1; H, 2·6; N, 26·7%).

(*c*) 6-Chloropteridine (0·05 g.) was shaken with 2N-sodium carbonate solution (5 ml.) for 15 min. The solution was treated with charcoal and filtered. The filtrate was adjusted to pH 5 with citric and sulphuric acid, and 6-hydroxypteridine (66%), identified by infrared spectroscopy, was filtered off.

Deformylation of 2-Formamidopyrazine Derivatives.—Finely ground 5,6-dichloro-2-formamido-3-formylpyrazine (VII) (0·025 g.) was shaken with 2N-sodium carbonate solution (2·5 ml.) at 20° for 1 hr. 2-Amino-5,6-dichloro-3-formylpyrazine (83%), m. p. 153°, was filtered off and shown by infrared spectroscopy to be identical with the specimen described above.

5- and 6-Chloro-2-formamido-3-formylpyrazine were deformylated similarly except for a shorter reaction time (15 min.), and the products were resublimed.

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Department of Medical Chemistry, Institute of Advanced Studies,
Australian National University,
Canberra, A.C.T., Australia. [*Received, September 30th,* 1963.]