945. *Pteridines. Part XXVII.*[1] *Dual Reactivity of Chloropteridines.*

By Jim Clark.

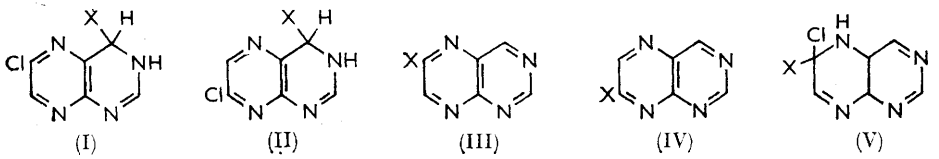
Nucleophiles, including ammonia, amines, and thiols, are shown to react with 6- and 7-chloropteridine in either of two ways, (*a*) by a rapid reversible addition across the 3,4-bond, or (*b*) by normal nucleophilic substitution of the chlorine atom. Under suitable conditions, either the adducts (I and II; X = NH_2, NHR, or S·CH_2Ph) or the substitution products (III and IV; X = NH_2, NHR, or S·CH_2Ph) can be isolated in good yield.

In solution, the adducts dissociate quantitatively into the original components by a reaction that is first order with respect to adduct for the substituted amines (I; X = NH·CH_2Ph or NH·cyclohexyl) in chloroform solution. The dissociation is greatly accelerated by acetic acid or cyclohexylamine but not by triethylamine.

It was shown recently that, in aqueous solution, 6- and 7-chloropteridine, and 6,7-dichloropteridine undergo rapid reversible addition of a molecule of water at the 3,4-double bond as well as normal nucleophilic replacement of a reactive chlorine atom.[2] This discovery suggested that attack at the 3,4-double bond as well as at the halogen atom may

[1] Part XXVI, Albert and Serjeant, *J.*, 1964, 3357.
[2] Albert and Clark, *J.*, 1964, 1666.

take place during reactions with other nucleophiles and may account for reported failures of chloropteridines to undergo certain simple replacement reactions.[3,4] The dual reactivity of the chloropteridines has now been confirmed by the preparation of new adducts and substitution products.



(I) (II) (III) (IV) (V)

6- and 7-Chloropteridine reacted with dry ammonia in benzene at 5° to yield 3 and 4-adducts, respectively (I and II; X = NH_2), which were shown by infrared spectroscopy, to contain little or none of the corresponding substitution product (III or IV; X = NH_2). The compounds decomposed slowly in air and almost instantaneously in water or ethanol to give the original chloropteridine and ammonia. When dissociation was complete, spectral comparison with pure 6- or 7-chloropteridine indicated that 95—97% of the chloro-compound had been re-formed (see Table 1). The amines were too unstable in all solvents examined for their ultraviolet spectra to be compared with those of corresponding hydrates, which are known to be 3,4-adducts.[2]

TABLE 1.

Ultraviolet absorption spectroscopy of pteridines.

Substance	Solvent	$\lambda_{max.}$ (mμ)	log ε	Assay (%)
6-Chloropteridine adducts				
I; X =				
NH_2				97 [b]
$NH{\cdot}CH_2Ph$	$CHCl_3$	274, 311, 325	3·63, 3·79, 3·74	101
NH·cyclohexyl	$CHCl_3$	274, 311, 324	3·63, 3·83, 3·75	100
$S{\cdot}CH_2Ph$	$CHCl_3$	281, 327	3·73, 3·63	97
OH	H_2O	236, 277, 330	3·74, 3·88, 3·93 [c]	
7-Chloropteridine adducts				
II; X =				
NH_2				95 [b]
$S{\cdot}CH_2Ph$	$CHCl_3$	341	3·96	94
OH	H_2O	238, 276, 327	3·62, 3·64, 4·02 [c]	
Pteridines				
6-Chloro	$CHCl_3$	304, 311, 317, 325	3·85, 3·96, 3·87, 3·93 [d]	
	cyclohexane	216, *244*, *285*, *291*, *298*, 303, 310, 316, 324	4·21, *3·56*, *3·46*, *3·61*, *3·77*, 3·84, 3·94, 3·88, 3·90 [e]	
$6\text{-}CH_2Ph{\cdot}S-$	$CHCl_3$	275, 368	4·22, 3·97	
	cyclohexane	*217*, 236, *266*, 274, *340*, 355, *367*	*4·07*, 4·07, *4·07*, 4·12, *3·76*, 3·90, *3·85*	
7-Chloro	$CHCl_3$	297, 304, 310, 318	3·91, 4·00, 3·96, 3·98 [d]	
	cyclohexane	*221*, *235*, *279*, *285*, *291*, *297*, 303, 309, 316	*4·02*, *3·54*, *3·52*, *3·69*, *3·82*, *3·91*, 3·99, 3·96, 3·92	
$7\text{-}CH_2Ph{\cdot}S-$	$CHCl_3$	246, *268*, 350	4·05, *3·86*, 4·16	
	cyclohexane	*216*, 245, *264*, *320*, *335*, 344, 359	*4·18*, 4·12, *3·89*, *3·79*, *4·04*, 4·16, 4·11	

[a] Percentage of 6- or 7-chloropteridine reformed when the adduct was allowed to dissociate in chloroform or [b] in pH 7 buffer (determined spectrophotometrically on each of three peaks and results averaged). [c] From ref. 2. [d] Inflections and shoulders omitted. [e] A less detailed spectrum was given in ref. 3.

The adduct derived from 6-chloropteridine and ammonia was prepared under conditions that are rather similar to those published for the preparation of 6-aminopteridine.[3] A re-investigation has shown that these conditions give a mixture of 6-aminopteridine (III;

[3] Albert, Brown, and Cheeseman, *J.*, 1952, 1620.
[4] Albert, Brown, and Wood, *J.*, 1954, 3832.

X = NH_2) and the adduct (I; X = NH_2) which, on crystallisation from water, gives a mixture of 6-amino- and 6-hydroxy-pteridine. A more satisfactory synthesis of 6-amino-pteridine was required and, in view of the instability of the unwanted adduct in water, the reaction between 6-chloropteridine and cold aqueous ammonia was tried and was successful. 7-Amino and 7-dimethylaminopteridine were formerly made from 7-methylthiopteridine,[4] but they are much more conveniently prepared from 7-chloropteridine by using cold aqueous ammonia or hot ethanolic dimethylamine.

Benzylamine and cyclohexylamine also reacted with 6-chloropteridine to give addition or substitution products. The new adducts (I; X = NH·CH_2Ph or NH·cyclohexyl) were more readily characterised than those derived from ammonia, since they could be stored

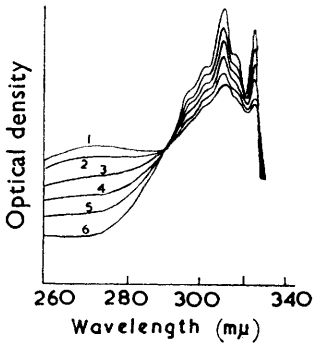


FIG. 1. Dissociation of 4-benzylamino-6-chloro-3,4-dihydropteridine ($8·3 \times 10^{-5}$M) in chloroform at 21°. Time from dissolution to start of scan at 260 mμ; curve 1, 8 sec.; 2, 45 sec.; 3, 130 sec.; 4, 220 sec.; 5, 340 sec.; 6, 20 min.

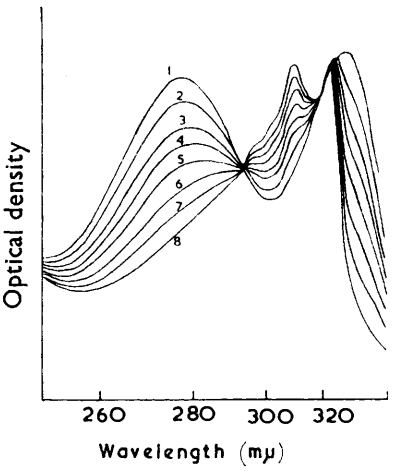


FIG. 2. Dissociation of 6-chloro-4-hydroxy-3,4-dihydropteridine (towards equilibrium), pH 6·9, 20°. Time from start; curve 1, continuous flow; 2, 9 min.; 3, 21 min.; 4, 31 min.; 5, 46 min.; 6, 70 min.; 7, 105 min.; 8, 270 min. (For experimental details see Ref. 2.)

for a few days at −20° and were more soluble in organic solvents. Ultraviolet spectra of the benzylamine and cyclohexylamine adducts were obtained by dissolving the substances in chloroform and rapidly scanning the spectrum several times. Extrapolation back to the time of dissolution gave reasonably accurate spectral values, although the half-lives of the compounds were only about 3 minutes (see Fig. 1 and Table 1). The spectral changes on dissociation closely resembled those observed during dissociation of 6-chloro-3,4-dihydro-4-hydroxypteridine (towards equilibrium) in water (Fig. 2) and provided strong evidence for the suggested structures.

The kinetics of dissociation of 4-benzylamino-6-chloro-3,4-dihydropteridine (I; X = NH·CH_2Ph) and 6-chloro-4-cyclohexylamino-3,4-dihydropteridine (I; X = NH·cyclohexyl) were investigated spectrophotometrically. The reactions were of the first order with respect to pteridine undergoing decomposition, but the rates increased with increase in concentration. For example, 4-benzylamino-6-chloro-3,4-dihydropteridine in chloroform at 21° had a half-life of 300 seconds when the initial concentration was $0·33 \times 10^{-4}$M, but this decreased to 105 seconds when the concentration was $1·1 \times 10^{-4}$M (see Experimental section). This suggests that the decomposition is catalysed by the adduct itself, and by the amine produced on dissociation; their combined concentration remains constant in any particular experiment.

Addition of one per cent of cyclohexylamine to the solvent greatly accelerated the dissociation and the addition of one per cent of acetic acid had an even greater effect, the dissociation now being complete within 2 seconds. Triethylamine, on the other hand, had very little effect on the dissociation rate, suggesting that a proton donor as well as a base is required. (The related covalent hydration reactions are subject to general acid and base catalysis.[5])

It was very difficult to separate addition and substitution reactions between 7-chloropteridine and powerfully nucleophilic amines. The benzylamine adduct (II; X = NH·CH_2Ph) was prepared in an almost pure state, but it discoloured appreciably in 30 minutes and was too unstable to be used conveniently. Cyclohexylamine caused appreciable substitution of 7-chloropteridine under all conditions examined.

Mercapto-derivatives.—6-Chloropteridine does not react with sodium hydrogen sulphide or thiourea in the normal way to yield 6-mercaptopteridine.[3] It has now been shown that treatment of 6- and 7-chloropteridine in acetone with hydrogen sulphide gives adducts of the type described above. Not these, but the more stable benzylthio-derivatives were characterised. 6-Chloropteridine and benzyl mercaptan in refluxing acetone (in the presence of potassium acetate) gave 6-benzylthiopteridine (III; X = S·CH_2Ph) (70%), and in benzene gave 4-benzylthio-6-chloro-3,4-dihydropteridine (I; X = S·CH_2Ph) (86%). 7-Chloropteridine gave similar yields of addition and substitution products.

The ultraviolet spectrum of 4-benzylthio-6-chloro-3,4-dihydropteridine (I; X = S·CH_2Ph) in chloroform closely resembled that of 6-chloro-3,4-dihydro-4-hydroxypteridine (I; X = OH) in water and again provided strong evidence for the suggested structure of the adduct. The infrared spectrum of the benzylthio-derivative was also consistent with structure (I; X = S·CH_2Ph), since it had no absorption maximum between 1600 and 2000 cm.$^{-1}$ and had a single intense peak in the NH stretching region at 3200 cm.$^{-1}$. 6-Chloropteridine (97%) was regenerated when the adduct was kept in chloroform solution for 24 hours (half-decomposition time ($t_{0.5}$) about 5 hours at 20°).

4-Benzylthio-7-chloro-3,4-dihydropteridine (II; X = S·CH_2Ph) decomposed rather more quickly in chloroform ($t_{0.5}$ about 30 minutes) to give 7-chloropteridine (93%). Infrared evidence for the suggested structure was less convincing than with the 6-chloro-isomer, since the highest frequency peaks in the spectrum were at 2700 and 2900 cm.$^{-1}$ [broad, fairly weak absorption between 2500 and 3000 cm.$^{-1}$ (KBr disc)]. The ultraviolet spectrum of the adduct dissolved in chloroform was rather similar, at the long-wavelength end, to that of the corresponding covalent hydrate (II; X = OH) in water. A less intense peak present at 276 mμ in the spectrum of the hydrate was absent from the spectrum of the mercaptan adduct

Conclusions.—The consequences of the interaction of 6- or 7-chloropteridine with a nucleophile are readily explained if rapid but reversible addition of the nucleophile to the 3,4-double bond of the chloro-compound accompanies the normal irreversible replacement of the chlorine atom. The addition reaction competes successfully, in a preparative sense, with the substitution reaction if the latter is slowed down by a low temperature and a non-polar solvent. Under these conditions, deposition of the adduct may disturb the equilibrium between it and its components and enable substantially complete conversion to the adduct to take place. The experimental conditions actually described were designed to give optimum purity rather than maximum yields of products.

It is considered likely that only 3,4-adducts are isolated in the reactions described above. Pteridine, 2-, 4-, and 7-methyl-pteridine [5,6] and the present compounds 6- and 7-chloropteridine [2] are all known to add water reversibly across the 3,4-double bond. Alternative structures such as (V) may describe intermediates in the replacement reactions,[7] but they would not be stable enough to isolate in the present cases nor would they revert completely

[5] Inoue and Perrin, *J.*, 1963, 2648.
[6] Perrin, *J.*, 1962, 645.
[7] Sauere and Huisgen, *Angew. Chem.*, 1960, **72**, 294.

to chloropteridines, since the chloride ion is a very efficient leaving group in nucleophilic substitution.[8]

Experimental

Ultraviolet spectra of benzyl mercaptan adducts (I and II; X = S·CH_2Ph) and chloropteridines, produced on dissociation of all adducts, were recorded on a Perkin-Elmer "Spectrocord" recording spectrophotometer. Spectra of amine adducts (I; X = NH·CH_2Ph or NH·cyclohexyl) were recorded on a Shimadzu model RS 27 spectrophotometer as follows: A small (arbitrary) quantity of adduct was dissolved directly in chloroform in the spectrometer cell and the spectrum scanned rapidly several times. The first scan was started within 10 sec. of dissolution and the recorded optical densities were extrapolated back to the time of dissolution. The concentration was determined by measuring the spectrum of the 6-chloropteridine produced when dissociation was complete. The dissociation was shown, in a separate experiment, to be quantitative (see Table 1).

The kinetics of the dissociation of the amine adducts (I; X = NH·CH_2Ph or NH·cyclohexyl) were studied spectrophotometrically by using the Shimadzu spectrophotometer with a thermostatted cell compartment in a constant temperature room. Changes in optical density in chloroform solution at a fixed wavelength of 270 mμ were followed

Approximate first order rate constants for dissociation of 4-benzylamino-6-chloro-3,4-dihydropteridine (I; X = NH·CH_2Ph) in chloroform (21°).

10^4 Concentration (M)	0·32	0·83	1·1	1·0 *
$10^3 K_{obs}$ (sec.$^{-1}$)	2·3	3·5	6·7	5·4 *

* Refers to cyclohexylamine adduct (I; X = NHcyclohexyl).

Preparation of Adducts.—*4-Benzylamino-6-chloro-3,4-dihydropteridine.* A cold (3°) solution of benzylamine (0·2 ml.) in dry benzene (2 ml.) was added to a solution of pure 6-chloropteridine (0·06 g.) in dry benzene (5 ml.) cooled until the benzene began to crystallise. The mixture was kept at 3—4° for 10 min., and filtered. The residue was washed with benzene, then thoroughly with light petroleum (b. p. 40—60°), and dried *in vacuo* for 5 min. at 20°. *4-Benzylamino-6-chloro-3,4-dihydropteridine* (71%) was obtained as crystals, which gradually decomposed when heated (Found: C, 56·7; H, 4·6; N, 25·3. $C_{13}H_{12}ClN_5$ requires C, 57·0; H, 4·4; N, 25·6%). Infrared spectroscopy failed to detect benzylamine hydrochloride or 6-benzylaminopteridine in the product.

The compounds in Table 2 were prepared similarly, from the relevant chloro-compound and nucleophile, except where noted otherwise.

Table 2.

Product	Temp.	Reaction time and m. p.	Yield (%)	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N
I; X = NH_2	5—8°	30 min.[a] decomp.	80	39·2	3·4	37·7	39·2	3·3	38·15
II; X = NH_2	5—8	30 min.[a] decomp.	73	38·9	3·3	37·7			
I; X = NH·cyclohexyl	3—4	20 min. decomp.	50	54·4	6·0	25·9	54·2	6·1	26·4
II; X = NH·CH_2Ph[b]	3—4	5 min. decomp.	46	56·6	4·6	25·0	57·0	4·4	25·6
I; X = S·CH_2Ph	5	24 hr.[c] 111° (dec.)	86	53·7	3·85	19·0	53·7	3·8	19·3
II; X = S·CH_2Ph	5	24 hr.[d] 116° (dec.)	86	53·4	3·8				

[a] Slow stream of dry NH_3 passed through a solution of the chloro-compound (0·25 g.) in dry benzene (40 ml.) at stated temp. for ½ hr. [b] Solid was unstable even at 0° and it discoloured appreciably in 30 min. at 20°; it contained a trace of benzylamine hydrochloride which was just detectable by infrared spectroscopy. [c] Solutions mixed at 50° and then refrigerated. [d] Solutions mixed at 20° and then refrigerated.

6-Aminopteridine. 6-Chloropteridine (0·33 g.) was stirred with aqueous ammonia (5 ml.; *d*, 0·91) for ½ hr. and kept at 5° for 24 hr. The solid was crystallised from water to yield 6-aminopteridine (65%) whose infrared spectrum was identical with that of an authentic specimen.[3]

7-Aminopteridine[4] (70%) was similarly prepared by treating 7-chloropteridine (0·5 g.) with aqueous ammonia (15 ml.; *d*, 0·91) at 20° for 1½ hr. 7-Chloropteridine and boiling ethanolic

[8] Bunnett and Zahler, *Chem. Rev.*, 1951, **49**, 273.

ammonia also gave a good yield of the amine, but 6-chloropteridine gave a dark green mixture under these conditions.

7-*Substituted aminopteridines.* 7-Chloropteridine (0·4 g.) was rapidly dissolved in boiling ethanol (5 ml.) and the relevant amine (0·8 ml.) was added. (For the dimethylamino-compound, 1 ml. of 33% w/v ethanolic dimethylamine was used). The mixture was heated under reflux for 15 min., and the yellow or cream-coloured solid that separated on cooling was crystallised from ethanol. (With 7-benzylaminopteridine, the crude solid was stirred with water (10 ml.) and refiltered before crystallisation from ethanol.)

			Found (%)			Required (%)		
Pteridine	M. p.	Yield (%)	C	H	N	C	H	N
7-Dimethylamino	205° (lit.,[4] 204°)	94						
7-Cyclohexylamino ...	252—254°	64	62·8	6·5	30·4	62·85	6·6	30·55
7-Benzylamino	202—203	83	65·4	4·7	29·6	65·8	4·7	29·5

6-*Cyclohexylaminopteridine.* 6-Chloropteridine (0·2 g.) was dissolved in ethanol (5 ml.) and the temperature of the solution adjusted to 50°. Cyclohexylamine (0·3 ml.) was added and the mixture was stored at 20° for 2 hr. The solvent was removed under reduced pressure and the residue was thoroughly mixed with cyclohexane and filtered. Ether (10 ml.) was added to the solid, insoluble matter filtered off, and the solution evaporated to dryness. Crystallisation of the residue from cyclohexane yielded 6-*cyclohexylaminopteridine* (51%) as yellow needles, m. p. 170—171° (Found: C, 62·85; H, 6·5; N, 30·8. $C_{12}H_{15}N_5$ requires C, 62·85; H, 6·6; N, 30·55%).

6-*Benzylaminopteridine.* Finely ground 6-chloropteridine (0·2 g.) was rapidly stirred with water (18 ml.) for 2 min. and benzylamine (0·4 ml.) added. Stirring was continued for 1 hr. during which lumps were broken up as required to give a smooth suspension. The precipitate was filtered off, dried, and crystallised from benzene ($MgSO_4$–charcoal) to yield 6-*benzylaminopteridine* (0·20 g.) as pale yellow needles, m. p. 199° (Found: C, 65·9; H, 4·8; N, 29·5. $C_{13}H_{11}N_5$ requires C, 65·8; H, 4·7; N, 29·5%).

6-*Benzylthiopteridine.* 6-Chloropteridine (1·5 g.), potassium acetate (3 g.), acetone (40 ml.), and benzyl mercaptan (1·2 g.) were heated under reflux for 10 min. The solvent was removed under reduced pressure and the residue thoroughly extracted with boiling light petroleum (b. p. 60—80°). The extract yielded 6-*benzylthiopteridine* (70%) as yellow prisms, m. p. 98—100° (raised to 100—101° by recrystallisation from light petroleum) (Found: C, 61·3; H, 3·9; N, 22·0. $C_{13}H_{10}N_4S$ requires C, 61·4; H, 4·0; N, 22·0%).

7-*Benzylthiopteridine* (75%) was obtained in the same way from 7-chloropteridine as yellow crystals, m. p. 112° (Found: C, 61·6; H, 4·05; N, 21·9%).

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