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CIBA FOUNDATION SYMPOSIUM
ON
CHEMISTRY AND BIOLOGY
OF PTERIDINES

Editors for the Ciba Foundation
and
MARGARET P. CAMERON, M.A., A.B.L.S.

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THE suggestion to hold a small, international conference for discussion of recent progress in research on pteridines originated with Dr. W. Jacobson of the Strangeways Laboratory, Cambridge. Prof. Adrien Albert, of the Australian National University (temporarily housed in London pending the construction of their laboratories in Canberra), was soon brought into consultation. The Director of the Ciba Foundation had very little hesitation in agreeing to provide an opportunity for a moderately informal, international symposium, on the lines of 24 others previously held at the Foundation. It was decided to cover both the chemical and biological aspects of pteridines, and Prof. Albert and Dr. Jacobson gave the Director most valuable advice respectively in the arrangement of the two halves of the symposium.

To those to whom this book serves as an introduction to the activities of the Ciba Foundation it should be explained that it is an international centre, which is established as an educational and scientific charity under the laws of England. It owes its inception and support to its founder, Ciba Ltd. of Switzerland, but is administered independently and exclusively by its distinguished British Trustees.

The Foundation provides accommodation for scientific workers who visit London from abroad, organizes and holds international symposia, conducts (in conjunction with the Institut National d'Hygiène) a postgraduate medical exchange scheme between England and France, arranges informal meetings for discussions, awards an annual lectureship, assists international congresses and other scientific societies, is building up a library service in special fields, and generally endeavours to give aid in all such matters as may promote international co-operation in scientific research.

Leading research workers from different countries and in different disciplines are invited to attend the symposia or
colloquia. The size of the groups is, however, very strictly limited in order to obtain a free conversational manner of discussion—although the basic timetable of the programme is strictly observed. The smallness of the groups necessarily means the exclusion of many other workers active and interested in the subjects discussed, and therefore the proceedings of these conferences are published and made available throughout the world.

It is hoped that the papers and discussions in this book will prove not only informative and stimulating, but will also give to readers a sense of participation in an informal and friendly occasion.

The tragic death soon after this Symposium, in a motoring accident, of Prof. M. Polonovski was a grievous blow to all who knew him as a man and as a scientist. We at the Foundation were grateful for this last opportunity to see him, and members of the Symposium, and others who read this book, may care to regard this work partly as a memorial to him. All will undoubtedly sympathize deeply with those, like Dr. Busnel, who had worked in close collaboration with him and were so suddenly bereft of his direction and advice.
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List of those participating in or attending the Symposium on “The Chemistry and Biology of Pteridines”, 22nd to 26th March, 1954.

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CHAIRMAN'S OPENING REMARKS

A. ALBERT

It is some sixty years since Sir Frederick Gowland Hopkins first began to extract pigments from butterflies. By a coincidence I was sitting next to his daughter, Mrs. Holmes, at lunch on Saturday, at the Biochemical Society's Annual Meeting. She said to me: "What worried Father for so many years was this: he wasn't sure that these pigments had real metabolic significance; he thought that they had." Luckily, before Sir Frederick died, seven years ago, he was able to see the Munich school work out the chemistry of these substances, and show that they were the very pyrimidopyrazines on which one or two organic chemists had been working for some years. Gowland Hopkins lived to hear of the discovery of folic acid, in America, and to see the trend of research which has led to the conclusion that pteridines are amongst the most important growth accelerating and growth determining agents known to man.

Just about two years ago Professor Polonovski called a number of pteridine workers to Paris, the first international Pteridine Conference that I know of, and it went very well. Today, thanks to the farsightedness and generosity of the Ciba Foundation, it has been possible to bring more people, even from great distances, and I am sure that at this meeting we can accomplish very valuable things. I feel that the chemists here have much of a fundamental nature to give the biologists, and the biologists can point out new pathways for the chemists to explore. It is most particularly to stimulate interactions of this kind between the various disciplines of learning that this conference has been called.
RING-OPENING REACTIONS OF PTERIDINES*

E. C. TAYLOR, Jr.

This paper is intended as a review of those reactions of pteridines which involve cleavage of either or both of the two rings in the pteridine ring system, and includes those ring-opening reactions which have been utilized for degradative purposes (such as proof of structure) or for the synthesis of pyrazines, pyrimidines, or pteridines, and those reactions occurring as intermediate steps in some other reaction. A discussion of the effect of structure on the ease and nature of the ring cleavage is also included. Since the in vivo utilization and synthesis of pteridines may involve ring-opening reactions, and the ultimate degradation as well as the (as yet hypothetical) in vivo transformation of pteridines into other heterocyclic systems, such as the purines, must involve ring-opening reactions, it is hoped that the present review will be of interest to those concerned with the biological as well as the chemical aspects of pteridine chemistry.

Probably every known pteridine may be cleaved by basic hydrolysis under sufficiently vigorous conditions. Since the pyrimidine portion of the ring is generally removed by this treatment and the resulting pyrazines are, in most cases, stable to alkali, the degradative process is of considerable importance as a synthetic route to pyrazines and often provides a useful means of establishing structure. The cleavage of substituted lumazines (2,4-dihydroxypteridines) to pyra-

*For details of cleavage reactions see pp. 13–33.
zines by hydrolysis with strong alkali was developed by Weijlard, Tishler and Erickson (1945) as a route to substituted 2-aminopyrazine-3-carboxylic acids. Decarboxylation of the latter compounds, effected by heating with sulphuric acid (or accomplished in one step by cleavage of the lumazine with sulphuric acid, *vide infra*), gives substituted 2-aminopyrazines. Thus, cleavage of lumazine (2,4-dihydroxypteridine) with 2-3 equivalents of 12 per cent sodium hydroxide for two hours at 170° gives 2-aminopyrazine-3-carboxylic acid in 93·5 per cent yield, while the use of stronger base for twenty-four hours gives 2-hydroxypyrazine-3-carboxylic acid in 91 per cent yield. 7-Methyl-, 6,7-dimethyl- and 6,7-diphenyllumazine are cleaved under similar conditions to the corresponding 2-aminopyrazine-3-carboxylic acids in yields of 31·4, 91·5 and 57 per cent respectively.

2-Amino-4-hydroxy- and 2,4-diaminopteridines may also be cleaved to pyrazines under similar conditions, and the reaction has been employed as a means of establishing the structure of various pteridine derivatives mono-substituted in the pyrazine ring. The decarboxylated product formed by condensation of 2,4,5-triamino-6-hydroxypyrimidine with methyl α,α-dimethoxyacetooacetate was cleaved with alkali to 2-amino-5-methylpyrazine-3-carboxylic acid, thus establishing the structure of the initial condensation product as 2-amino-4-hydroxypteridine-6-acetic acid (Mowat et al., 1948); this result was an important part of the fundamental structural work on folic acid. Similarly, the reaction product of 2,4,5-triamino-6-hydroxypyrimidine and methyl glyoxal acetal was shown to be 2-amino-4-hydroxy-7-methylpteridine by cleavage to 2-amino-6-methylpyrazine-3-carboxylic acid (Mowat et al., 1948). The latter pyrazine was also obtained by alkaline cleavage of the reaction product of 2,4,5,6-tetraminopyrimidine and methyl glyoxal, thus establishing the structure of the product as 2,4-diamino-7-methylpteridine (Cain, Mallette and Taylor, 1948). The product of the condensation of 2,4,5-triamino-6-hydroxypyrimidine bisulphite with phenyl glyoxal and with α-nitroacetophenone was
shown to be 2-amino-4-hydroxy-7-phenylpteridine by alkaline hydrolysis to a mixture of 2-hydroxy- (20 per cent yield) and 2-amino-6-phenylpyrazine-3-carboxylic acids (50 per cent yield). Likewise, the product of the condensation of 2,4,5-triamino-6-hydroxypyrimididine bisulphite with $\omega,\omega$-dichloroacetophenone was shown to be the isomeric 2-amino-4-hydroxy-6-phenylpteridine by cleavage to 2-amino-5-phenylpyrazine-3-carboxylic acid (57 per cent yield) (King and Spensley, 1952).

Examples are known which involve similar cleavages of condensed 2,4-dihydroxypteridine systems. 2,4,5,7-Tetrahydroxypyrimido(5,4-g)pteridine (bis-alloxazine) is cleaved with 15 per cent sodium hydroxide at 170° for three hours to 2,6-diaminopyrazinedicarboxylic acid, and 2,4,6,8-tetrahydroxypyrimido(4,5-g)pteridine is cleaved under similar conditions to 2,5-diaminopyrazinedicarboxylic acid.

The cleavage of 4-hydroxypteridines with alkali takes place under milder conditions than are necessary for the cleavage of 2,4-dihydroxy-, 2-amino-4-hydroxy- or 2,4-diaminopteridines. 4-Hydroxypteridine is hydrolysed to 2-aminopyrazine-3-carboxylic acid by 10 N sodium hydroxide at 110° (Albert, Brown and Cheeseman, 1952). The structure of the product formed by the condensation of 4,5-diamino-6-hydroxypyrimidine and methyl glyoxal in the presence of sodium sulphite was shown to be 4-hydroxy-7-methylpteridine by cleavage with 10 N sodium hydroxide for four hours at 140° to give 2-amino-6-methylpyrazine-3-carboxylic acid in 70 per cent yield, while the structure of the product formed from the same reagents in the presence of sodium hydrogen sulphite was shown to be the isomeric 4-hydroxy-6-methylpteridine by cleavage under similar conditions to 2-amino-5-methylpyrazine-3-carboxylic acid in 80 per cent yield (Albert, Brown and Cheeseman, 1952). Treatment of 4,7-dihydroxypteridine-6-carboxylic acid with 1 N sodium hydroxide resulted in rapid ring cleavage to give an unidentified product believed to be a derivative of 2-aminopyrazine-3-carboxylic acid. The same product was formed in unspecified yield when the above
pteridine was boiled with water for fifteen minutes (Albert and Brown, 1953).

Pteridine itself is cleaved by boiling with 1 N potassium hydroxide for one hour, although no product was isolated from the hydrolysis, and 2-hydroxy-, 2-amino- and 2-dimethylaminopteridine are destroyed by boiling with 1 N sodium hydroxide for one minute (Albert, Brown and Cheeseman, 1951). The lability of these compounds in contrast to the remarkable stability of tetrasubstituted derivatives such as leucopterin has been attributed to an electron deficiency inherent in the unsubstituted pteridine nucleus which arises from localization of the ten π electrons, available for aromatic stabilization from the four nitrogen atoms and the six carbon atoms, on the electron-attracting heteroatoms. It has been suggested that the resulting state of electron deficiency might be evidenced by lack of co-planarity of pteridine (Albert, 1952). Substitution into the nucleus in positions 2,4,6 or 7 of electron-releasing groups redresses the electron deficiency to a greater or lesser extent and thus helps to restore normal aromatic stability. Thus, the stability of any pteridine derivative, particularly to nucleophilic attack, would appear to be directly related to the ability of its substituent groups to restore the electron deficiency inherent in the unsubstituted nucleus. The stability to cleavage by base or other nucleophilic species therefore increases as the number of amino, substituted amino, hydroxy, halogen, mercapto or similar substituents increases. (This point has also been discussed by Albert (1952)).

Although 4-hydroxy-6,7-diphenylpteridine may be cleaved by alkali under strenuous conditions (10 N sodium hydroxide at 100° for thirty hours) to 2-amino-5,6-diphenylpyrazine-3-carboxylic acid, it is completely stable to mild alkali, since formation of a simple anion stabilizes the ring with respect to further attack by dilute alkali. 3-Benzyl-6,7-diphenyl-4 (3H)-pteridinone, on the other hand, which no longer possesses an acidic hydrogen and thus cannot form a simple anion, is
extremely labile to alkali and is cleaved to \( N \)-benzyl-2-amino-5,6-diphenylpyrazinamide in 87.5 per cent yield by short heating with 0.01 \( \text{N} \) potassium hydroxide in methanol solution (Taylor, 1952c). The mechanism of this hydrolysis would appear to involve initial attack of the hydroxyl ion at \( C(2) \), followed by ring opening to give an \( N \)-formylpyrazinamide or a 2-formylaminopyrazinamide and subsequent elimination of sodium formate by hydrolysis. In a similar manner, 2,6,7-triphenyl-8-benzyl-4(3\( H \))-pteridinone and 2-methyl-6,7-diphenyl-3-benzyl-4(3\( H \))-pteridinone are readily hydrolysed to \( N \)-benzyl-2-amino-5,6-diphenylpyrazinamide by heating with sodium ethoxide, and 1-benzyl-6,7-diphenyl-4(1\( H \))-pteridinone is smoothly cleaved to 2-benzylamino-5,6-diphenylpyrazinamide.

As further examples of this lability to hydrolysis in more highly condensed systems, 1,3,6,8-tetramethyl-2,4,5,7(1\( H \),3\( H \),6\( H \),8\( H \))-pyrimido(5,4-g)pteridinetetrone is cleaved with 1 \( \text{N} \) sodium hydroxide at 100° for three hours to 2,6-bis(methylamino)-\( N \)-methyl-\( N' \)-methylpyrazine-3,5-dicarboxamide in 81 per cent yield, and 1,8,5,7-tetramethyl-2,4,6,8(1\( H \),3\( H \),5\( H \),7\( H \))-pyrimido(4,5-g)pteridinetetrone is cleaved to a mixture of 2,5-bis(methylamino)pyrazine-3,6-dicarboxylic acid (34 per cent) and 2,5-bis(methylamino)-\( N \)-methyl-\( N' \)-methylpyrazine-3,6-dicarboxamide (34 per cent).

Only a few examples are known of cleavage of the pyrazine ring in preference to the pyrimidine ring. 7-Hydroxypteridine is cleaved to 4,5-diaminopyrimidine in 42 per cent yield (much starting material is recovered) by two equivalents of \( \text{N} \) sodium hydroxide at 100° for four hours, while acid hydrolysis results predominately in cleavage of the pyrimidine ring to give (presumably) 2-amino-6-hydroxypyrazine-8-aldehyde, although a little 4,5-diaminopyrimidine is formed as well (Albert, personal communication). 7-Hydroxy-5,6-dihydroppteridine is cleaved instantaneously in greater than 95 per cent yield to 4-amino-5-carboxymethylaminopyrimidine by boiling \( \text{N} \) sodium hydroxide (Albert, Brown and Cheeseman, 1952a). 8-Methyl-7(8\( H \))-pteridinone and 6,8-dimethyl-7(8\( H \))-
pteridinone are cleaved to 4-methylamino-5-aminopyrimidine in 94 and 90 per cent yields respectively by boiling Na sodium hydroxide for two hours (Wood, personal communication).

It would appear that dihydopteridines are more readily cleaved than the parent pteridine. Thus, in addition to the rapid hydrolysis of 7-hydroxy-5,6-dihydropteridine mentioned above, dihydroxanthopterin appears to be somewhat more readily cleaved by acid to glycine than is xanthopterin (Schöpf, Becker and Reichert, 1939). However, complete reduction of the pyrazine ring restores stability to the system (which is thus converted to a substituted 4,5-diaminopyrimidine); pteridine is extremely unstable towards dilute acid, base or light, but 5,6,7,8-tetrahydropteridine is completely stable under similar conditions.

Those pteridines which undergo cleavage with alkali should undergo cleavage with other nucleophilic reagents under suitable conditions, and the structural features influencing the degree of lability towards alkali should govern the latter cases as well. Thus, lumazines (2,4-dihydroxypteridines) are readily cleaved to pyrazinamides by heating with amines. 2,4-Dihydroxy-6,7-diphenylpteridine is cleaved by short heating with benzylamine to give $N$-benzyl-2-(3-benzylureido)-5,6-diphenylpyrazinamide in 41.5 per cent yield, while longer heating with benzylamine leads to cleavage of the ureido substituent to give $N$-benzyl-2-amino-5,6-diphenylpyrazinamide in 60 per cent yield. Similarly, cleavage of 2,4-dihydroxy-6,7-diphenylpteridine with piperidine in refluxing dimethylformamide gives 2-(piperidinocarbonylamino)-5,6-diphenylpyrazinoic acid piperidide in 39.5 per cent yield, while heating the same reactants in a sealed tube at 200° gives 2-amino-5,6-diphenylpyrazinoic acid piperidide in 67 per cent yield. Cleavage with hydrazine gives a mixture of 2-amino-5,6-diphenylpyrazinoic acid hydrazide (73 per cent yield) and a small amount of 3-amino-6,7-diphenyl-2,4(1H, 3H)-pteridinedione, the latter presumably being formed by recyclization of the intermediate cleavage product, 2-ureido-5,6-diphenylpyrazinoic acid hydrazide. Numerous other
aminolysis reactions of 2,4-dihydroxy-6,7-diphenylpteridine have been described and the mechanism of the cleavage has been discussed in detail (Taylor, 1952b). It appears that the initial ring cleavage occurs at the $N_3-C_4$ linkage as a result of nucleophilic attack of the amine at $C_4$. This gives rise to a 2-ureidopyrazine-3-carboxamide which undergoes immediate aminolysis to give the first isolated product, a 2-(substituted ureido)-pyrazine-3-carboxamide. Further aminolysis of the latter leads to the final products, a substituted 2-aminopyrazine-3-carboxamide and a sym-disubstituted urea.

The reaction of 2-mercapto-4-hydroxy- and 2-mercapto-4-aminopteridines with alkyl amines has been shown to give 2,4-bis(alkylamino)pteridines under appropriate conditions, and it has been suggested that the formation of such products involves preliminary ring opening of the pteridine to an intermediate thioureido pyrazine which undergoes subsequent aminolysis followed by ring re-closure to give the observed product (Taylor and Cain, 1951). The action of alkyl amines on 2,4-diamino-pteridines has been shown to give 4-alkylamino-2-aminopteridines in the absence of acid, and 2,4-bis-(alkylamino)pteridines in the presence of a trace of mineral acid. These aminolysis reactions have also been postulated to involve intermediate ring opening followed by recyclization (Taylor, 1952a).

4-Hydroxypteridines are also cleaved to pyrazinamides by heating with amines. 4-Hydroxy-6,7-diphenylpteridine is cleaved to 2-amino-5,6-diphenylpyrazinamide in 96 per cent yield by heating with ammonium hydroxide at 180° for four hours. Similarly, 4-hydroxy-6,7-diphenylpteridine is cleaved by hydrazine, benzylamine and morpholine to give the hydrazide, the $N$-benzylamide and the morpholide respectively of 2-amino-5,6-diphenylpyrazine-3-carboxylic acid, all in yields over 85 per cent.

The initial step in the cleavage of a 4-hydroxypteridine with an amine appears to be nucleophilic attack by the amine at the $C_2-N_3$ (amidine) linkage rather than at the $N_3-C_4$
RING-OPENING REACTIONS OF PTERIDINES

(amide) linkage. This view is supported by the observation that the reaction of 4-hydroxy-6,7-bis(p-chlorophenyl)pteridine with isopropyl amine gives \( N \)-isopropyl-2-amino-5,6-bis(p-chlorophenyl)pyrazinamide at 200° but 2-amino-5,6-bis(p-chlorophenyl)pyrazinamide at 150°.

It is pertinent to the present discussion to point out that 4-hydroxyquinazoline, which differs from 4-hydroxypteridine in having a benzene ring rather than a pyrazine ring fused to the pyrimidine ring, does not undergo analogous ring cleavage when heated with amines, but rather replacement at \( N_{(3)} \) to give 3-alkyl- or 3-aryl-4(3H)-quinazolones (Leonard and Curtin, 1946). 6-Nitro- and 8-nitro-4-hydroxyquinazolines, on the other hand, undergo ring cleavage in the same fashion as 4-hydroxypteridines to give \( N \)-substituted 3- and 5-nitro-anthranilic acid amides. (It has been shown here as well that the cleavage is initiated by nucleophilic attack of the amine at the \( C_{(2)}-N_{(3)} \) linkage.) Furthermore, 5- and 7-nitro-4-hydroxyquinazolines undergo nucleophilic replacement of the \( Bz \)-nitro group by the amine rather than ring cleavage or replacement at \( N_{(3)} \). Thus, the presence of an electron-withdrawing group in the 6- or 8-position of the quinazoline nucleus, but not in the 5- or 7-position, labilizes the pyrimidine ring towards aminolytic cleavage. One is led to the intriguing postulate that the \( N_{(8)} \) but not the \( N_{(5)} \) hetero-nitrogen atom in the pteridine nucleus may be responsible for the lability of the pyrimidine ring of 4-hydroxypteridines towards nucleophilic attack. An attempt to settle this question is now being made by a study of the behaviour towards aminolysis of all four of the isomeric 4-hydroxypyrimidopyridines.

Pteridines may also be cleaved with acids, although in some instances the cleavage is more difficult than with base and may even bring about complete disruption of the compound. Acid cleavage is also not as general as alkaline cleavage. For example, although 2,4-dihydroxy-7-phenylpteridine is cleaved to 2-amino-6-phenylpyrazine (although only in 14·5 per cent yield) by 80 per cent sulphuric acid at 200° (Weijlard, Tishler and Erickson, 1945), 2-amino-4-hydroxy-7-phenylpteridine
E. C. TAYLOR, JR.

is completely stable under similar conditions (King and Spensley, 1952). In general, however, sulphuric acid degra-
dation of lumazines may be considered to be a preparative
route to aminopyrazines; lumazine, 6,7-dimethyl-, 6,7-
diphenyl- and 7-methyllumazine are all cleaved to the
corresponding aminopyrazine in strong, hot sulphuric acid
solution. Nevertheless, the direct synthesis of an amin-
opyrazine by this method often results in lower yields than
the two-step process involving initial alkaline cleavage to a
2-aminopyrazinoic acid followed by decarboxylation
(Weijlard, Tishler and Erickson, 1945).

Pteridine itself is hydrolysed by N sulphuric acid in five
minutes at 120° to 2-aminopyrazine-3-carboxaldehyde in good
yield (60 per cent isolated as the free aldehyde, 85 per cent
isolated as the oxime) (Albert, personal communication).
4-Hydroxypteridine is cleaved by N sulphuric acid to a
mixture of 2-amino-3-pyrazinamide and 2-aminopyrazinoic
acid, and 3-methyl-4(3H)-pteridinone is cleaved readily by
cold N hydrochloric acid to give (presumably) 2-amino-N-
methyl-3-pyrazinamide (Albert, Brown and Cheeseman,
1952b).

Acid hydrolysis may lead to complete disruption of the
molecule if the pyrazine ring carries a hydroxyl substituent.
Xanthopterin (2-amino-4,6-dihydroxypteridine) is cleaved to
glycine by 4 N hydrochloric acid at 200° for five hours (Schöpf,
Becker and Reichert, 1939), and leucopterin (2-amino-4,6,7-
trihydroxypteridine) is cleaved to glycine, carbon dioxide,
carbon monoxide and ammonia by 10 N hydrochloric acid at
160–170° for five hours (Wieland, Metzger, Schöpf and Bülow,
1933). As mentioned above, dihydroxanthopterin is also
hydrolysed to glycine.

Oxidative hydrolysis usually leads to cleavage of both the
pyrimidine and the pyrazine ring, and this method of degrada-
tion was widely applied in the early structural work on the
naturally-occurring pteridines. Xanthopterin is cleaved by
sodium chlorate and hydrochloric acid at 80° for five minutes
to a mixture of oxalylguanidine, oxalic acid, guanidine,
ammonia and carbon dioxide, while the same reagents at 100° for twelve minutes give guanidine, oxalic acid, glyoxylic acid, urea, ammonia and carbon dioxide (Schöpf and Kottler, 1939). The same reagents at 80° for one hour cleave 2-amino-4-hydroxypteridine-6-carboxylic acid to guanidine (Wittle, O’Dell, Vandenbelt and Pfiffner, 1947).

A number of cleavage reactions of xanthopterin and leucopterin are known which involve the hydrolysis of the corresponding 9,10-glycol, which may or may not be an isolated intermediate. 2,4,6,7-Tetrahydroxypteridine is converted to 5-methoxyuramil-7-oxalic acid methyl ester with chlorine in methanol, presumably via the intermediate formation of the “glycol ether” (Wieland and Tartter, 1940). Leucopterin glycol, prepared by the action of chlorine on leucopterin, is cleaved with 0.1 N hydrochloric acid at 140–150° for three hours to ammonium hydrogen oxalate, guanidine and carbon dioxide (Wieland, Metzger, Schöpf and Bülow, 1933). Hydrolysis of leucopterin glycol with lithium hydroxide gives 2-imino-hydantoin-5-oxamide, 2-imino-hydantoin-5-oxamic acid, 2-imino-5-aminohydantoin and oxalic acid. This transformation probably occurs by initial ring cleavage at $C(8)-N(9)$ to give 5-hydroxyuramil-7-oxamide. (It should be pointed out that this structure has never been excluded for leucopterin glycol itself and may represent its correct structure) (see Wieland and Purrman, 1940.) An alkaline-catalysed β-diketone cleavage followed by decarboxylation of the resulting carbamic acid and ring re-closure would give 2-imino-hydantoin-5-oxamide, while hydrolysis of the latter would give rise to the additional products isolated.

The degradation of xanthopterin, leucopterin and 2-amino-4-hydroxypteridine-6-carboxylic acid to guanidine by treatment with chlorine in aqueous solution followed by hydrolysis with 0.1 N hydrochloric acid at 140° for three hours probably proceeds by way of the intermediate formation of the corresponding glycol (Stokstad et al., 1948).

A few miscellaneous ring-cleavage reactions of pteridines have been reported. Xanthopterin is cleaved to a mixture of
oxalylguanidine, oxalic acid and guanidine by treatment with ozone in dilute alkali (Schöpf and Kottler, 1939). It has been reported that hydrogen peroxide at 100° for five minutes converts xanthopterin into 2-iminohydroxonic acid (Wieland and Purrman, 1940), while the same reagent at 100° for one hour was reported to convert xanthopterin peroxide (probably xanthopterin-8-oxide, and formed by the action of hydrogen peroxide in glacial acetic acid on xanthopterin) to 2-amino-4,6-dihydroxy-1,3,5-triazine (melanurenic acid) (Wieland and Purrmann, 1939).

One of the most remarkable ring-cleavage reactions observed is the smooth conversion of 4-mercapto-6,7-diphenylpteridine to 2-amino-3-cyano-5,6-diphenylpyrazine in 95.5 per cent yield with chloroacetic acid and potassium carbonate. The mechanism of this transformation has not been elucidated, but it has been shown that the corresponding pyrazinethioamide is not an intermediate in the conversion and that thio-glycollic acid is one of the cleavage products.
### Ring-Cleavage Reactions of Pteridines

**A. Cleavage with Alkali**

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Temp.</th>
<th>Time</th>
<th>Yield</th>
<th>Ref.</th>
</tr>
</thead>
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<td>10 N NaOH</td>
<td>100° C</td>
<td>15 min.</td>
<td>-</td>
<td>6</td>
</tr>
<tr>
<td>10 N NaOH</td>
<td>140° C</td>
<td>3 hr.</td>
<td>80%</td>
<td>6</td>
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<td>10 N NaOH</td>
<td>140° C</td>
<td>4 hr.</td>
<td>70%</td>
<td>6</td>
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<tr>
<td>H₂O</td>
<td>100° C</td>
<td>15 min.</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>n NaOH</td>
<td>warm</td>
<td>-</td>
<td>-</td>
<td>3</td>
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</tbody>
</table>

**Pteridine**

![Pteridine structures]

**Product**

- ![NH₂-COOH](image1)
- ![NH₂-COOH](image2)
- ![NH₂-COOH](image3)
- ![NH₂-COOH](image4)

**Derivative of**

- ![NH₂-COOH](image5)

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*Ref.* indicates references for further reading.
<table>
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<tr>
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<th>Time</th>
<th>Yield</th>
<th>Ref.</th>
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<tbody>
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<td>100°</td>
<td>30 hr.</td>
<td>82%</td>
<td>14</td>
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<tr>
<td>0.01 N KOH</td>
<td>65°</td>
<td>10 min.</td>
<td>87.5%</td>
<td>17</td>
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<td>in CH₃OH</td>
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<tr>
<td>NaOEt</td>
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<tr>
<td>Reflux 3 hr.</td>
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<tr>
<td>NaOEt</td>
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<td></td>
<td></td>
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<tr>
<td>Reflux 3 hr.</td>
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**Product**

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<tbody>
<tr>
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**Piperidine**

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*Note: The diagrams are not fully transcribed and may require further clarification.*