Heterocyclic Studies. Part I. Ring-opening of Some 4-Hydroxypteridine Derivatives

By Jim Clark and G. Neath

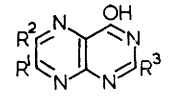
4-Hydroxypteridine and its *C*-methyl derivatives, without a 2-substituent, yielded 3-aminopyrazine-2-carboxylic acids readily when treated with alkali. When a 2-methyl group was present ring-opening was greatly retarded. Treatment of each pteridine with hydrazine gave a mixture of a 4,5-diaminopyrimidine and a 3-aminopyrazine-2-carbohydrazide, unless a 7-methyl group was present, in which case no pyrimidine derivative was formed. The positions of attack on the pteridine molecule by the reagents are discussed.

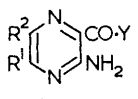
RING-OPENING of heterocyclic compounds which consist of a 4-hydroxypyrimidine (or 4-pyrimidone) system fused to another ring has attracted considerable interest. Those in which ring-opening has been observed include 4-hydroxypteridines (I),[1-5] 6-hydroxypurines,[6,7] 4-hydroxyquinazolines,[8] 7-hydroxy-[1,2,5]-thiadiazolo[3,4-*d*]-

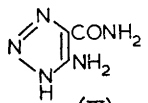
[1] A. Albert, D. J. Brown, and G. Cheeseman, *J. Chem. Soc.*, 1952, 4219.
[2] A. Albert, *J. Chem. Soc.*, 1955, 2690.
[3] J. Weijlard, M. Tishler, and A. E. Erickson, *J. Amer. Chem. Soc.*, 1945, **67**, 802; E. C. Taylor, jun., J. A. Carbon, and D. R. Hoff, *ibid.*, 1953, **75**, 1904.
[4] E. C. Taylor, jun., *J. Amer. Chem. Soc.*, 1952, **74**, 1651.
[5] E. C. Taylor, jun., in "Chemistry and Biology of Pteridines," ed. G. E. W. Wolstenholme and M. P. Cameron, Churchill, London, 1953, p. 2.
[6] E. Shaw, *J. Amer. Chem. Soc.*, 1958, **80**, 3899; 1959, **81**, 6021.
[7] H. Biltz and H. Rakett, *Ber.*, 1928, **61**, 1409; L. B. Townsend and R. K. Robins, *J. Amer. Chem. Soc.*, 1963, **85**, 242.
[8] N. J. Leonard and D. Y. Curtin, *J. Org. Chem.*, 1946, **11**, 341; N. J. Leonard, W. V. Ruyle, and L. C. Bannister, *ibid.*, 1948, **13**, 903.

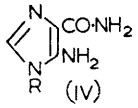
pyrimidines,[9] 8-azaxanthine,[10] triazaindolizines,[11] and pyrido[3,2-*d*]pyrimidin-4(3*H*)-ones.[12]

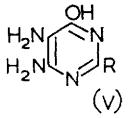
Treatment of these compounds with nucleophiles such as hydroxide ion, ammonia, amines, and hydrazine has almost invariably led to rupture of the pyrimidine ring. Many different heterocyclic systems are involved, but it is clear that, mechanistically, the reactions have many features in common. In several instances this very general type of ring-cleavage has been used to prepare otherwise inaccessible compounds. For example, substituted 3-aminopyrazine-2-carboxyamides (II; Y = NH_2 or NHR) were prepared from lumazines (I; R^3 = OH),[4] 4-amino-5-carbamoyl-1,2,3-triazole (III) from 8-azaxanthine,[10] and 4-amino-5-carbamoylimidazoles (IV) from hypoxanthine derivatives.[6]

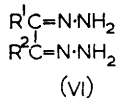

(I)

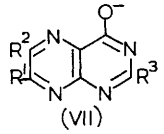

(II)


(III)


(IV)


(V)


(VI)


(VII)

It is now shown that, in the case of 4-hydroxypteridines, the pattern of ring-opening can be substantially changed by altering the nucleophile or the alkyl substitution pattern in the pteridine nucleus. 4-Hydroxypteridine and all possible mono-, di-, and tri-*C*-methyl derivatives are compared. Of these, only 2,6- and 2,7-dimethyl-4-hydroxypteridine have not been described. The former (I; $R^2 = R^3 = Me$, $R^1 = H$) was synsynthesised from 2-amino-3-carbamoyl-5-methylpyrazine and ethyl orthoacetate, and the latter (I; $R^1 = R^3 = Me$, $R^2 = H$) from the pyrimidine (V; R = Me) and methylglyoxal. The last reaction could also have led to the 2,6-isomer but it was shown that very little, if any, of this was formed under the conditions used.

Other workers had shown that 4-hydroxypteridine and its 6- and 7-methyl derivatives yield 3-aminopyrazine-2-carboxylic acids (II; Y = OH) on vigorous alkaline hydrolysis.[1,2] Similar ring-openings have now been carried out on other *C*-methyl derivatives. The conversion into pyrazines was rapid and essentially quantitative, except for the four compounds with a 2-methyl group (I; R^3 = Me). These were only gradually changed by boiling 2N-sodium hydroxide, and in several cases ring-opening was incomplete after 72 hours. In no case could any of the pyrimidine derivative (V; R = Me), which would arise from cleavage of a pyrazine ring, be detected.

Each of the eight 4-hydroxypteridines (I) was also treated with refluxing hydrazine hydrate, to give a mixture of products which typically contained a 3-aminopyrazine-2-carbohydrazide (II; Y = $NH{\cdot}NH_2$), a 4,5-diamino-6-hydroxypyrimidine (V), and the dihydrazone (VI) of a dicarbonyl compound. The compositions of the mixtures were determined qualitatively by isolating the major products and demonstrating the presence of minor products by thin-layer chromatography on silica gel. In some cases the hydrazides were more conveniently isolated as isopropylidene derivatives (II; Y = $NH{\cdot}N{:}CMe_2$). Each ring-opening was repeated, and the proportions of products in the whole reaction mixture were determined by ultraviolet spectroscopy.

The results (Table 1) show that the pattern of ring-opening with hydrazine hydrate is quite different from that with sodium hydroxide. However, the methyl substitution pattern had a marked effect on the position and ease of ring-opening in both cases, and this throws some light on the mechanism of the reactions.

Methyl groups are known to reduce the rate of covalent hydration of pteridines (as well as affecting equilibria) when they are situated at the site of water addition, but to have less effect from other positions. For example, the methyl group in 6-hydroxy-7-methylpteridine substantially reduces the rate of water addition to the 7,8-bond, while 2- and 4-methyl groups are relatively ineffective.[13]

Both the covalent-hydration reactions and the present ring-openings probably involve nucleophilic attack at a polarised C=N linkage, so the effect of methyl groups is likely to be qualitatively similar. Thus, the powerful effect of a 2-, but not a 6- or 7-, methyl group (Table 1) indicates that pyrimidine ring-opening of our compounds, by alkali, involves attack at the 2-position. This is expected because, in sodium hydroxide solution, the pteridines (p*K* values in Table 2) are present almost entirely as anions (VII) in which electrostatic repulsion protects the 4-position from attack by hydroxide ions. Structural modifications which prevent ionisation are well known to make hydroxy-heterocycles more labile to alkali.[5,6,14,15]

The effect of a 7-methyl group which completely stops pyrazine ring-opening (Table 1), similarly indicates that opening of this ring by hydrazine involves nucleophilic attack at the 7-position.

The position of attack by hydrazine on the pyrimidine ring is less certain, since a 2-methyl group had little effect when this reagent was used. Related cleavages have been stated to occur by initial reaction at the 2-position,[5,6,14] the 4-position,[4,5,8] or both the 2- and the 4-position.[16]

In the present cases, attack by hydrazine appears to have been mainly at the 4-position. Cleavage at the

[9] Y. F. Shealy and J. D. Clayton, *J. Org. Chem.*, 1963, **28**, 1491.
[10] L. L. Bennett and H. T. Baker, *J. Org. Chem.*, 1957, **22**, 707.
[11] F. Baumbach, H. G. Henning, and G. Hilgetag, *Z. Chem.*, 1962, **2**, 369.
[12] W. J. Irwin and D. G. Wibberley, *J. Chem. Soc.*, 1965, 4240.
[13] Y. Inoue and D. D. Perrin, *J. Chem. Soc.*, 1963, 4803.
[14] W. Curran and R. B. Angier, *J. Org. Chem.*, 1961, **26**, 2364.
[15] E. Fischer, *Ber.*, 1898, **31**, 3266; A. Albert, D. J. Brown, and H. C. S. Wood, *J. Chem. Soc.*, 1956, 2066; E. C. Taylor, O. Vogl, and P. K. Loeffler, *J. Amer. Chem. Soc.*, 1959, **81**, 2479; E. C. Taylor, jun., *ibid.*, 1952, **74**, 2380.
[16] H. C. S. Wood, ref. 5, p. 35.

TABLE 1

Ring-opening of 4-hydroxypteridine derivatives

4-Hydroxypteridine (I) R¹	R²	R³	Reagent *	Approximate yield of products (%) † Pyrazine-2-carboxylic acid (II; Y = OH) ‡	4,5-Diamino-pyrimidine (V) ‡	Unchanged pteridine (I) ‡	Reaction time (hr.)
H	H	H	A	100			1·5
Me	H	H	A	100			2·5
H	Me	H	A	98			2·5
Me	Me	H	A	95			6·5
H	H	Me	A	99			72
H	Me	Me	A	76		24	72
Me	H	Me	A	75		25	72
Me	Me	Me	A	52		48	72
				Pyrazine-2-carbohydrazide (II; Y = NH·NH₂) ‡			
H	H	H	Hy	20	80		
Me	H	H	Hy	100 §			
H	Me	H	Hy	47	53		
Me	Me	H	Hy	95 §			
H	H	Me	Hy	12	88		
H	Me	Me	Hy	27	73		
Me	H	Me	Hy	90 §			
Me	Me	Me	Hy	91			

* A = Boiling 2N-sodium hydroxide; Hy = 98—100% hydrazine hydrate on a water bath. † Determined by ultraviolet spectroscopy. ‡ R¹, R², R³ as in starting compound. § Contains a little of the corresponding carboxyamide.

TABLE 2

Spectra and ionisation constants

4-Hydroxypteridine (I)	Ionisation (H_2O, 20°) [a] pK_a and spread	Anal. λ(mμ)	Spectroscopy in water Species [b]	λmax. (mμ)			log ε			pH
6-Methyl	8·19 ± 0·02[1]		0	230	265	317	4·03	3·77	3·89	5·6
			—	244	337		4·28	3·83		10·9
7-Methyl	8·09 ± 0·03[1]		0 [c]	232	270	311	4·05	3·63	3·93	5·6
			— [c]	244	331		4·24	3·83		10·9
2-Methyl	8·57 ± 0·04		0	230	266	315	4·04	3·69	3·83	6·5
			—	243	335		4·28	3·78		11·3
2,6-Dimethyl	8·97 ± 0·06		0	234	266	320	3·99	3·78	3·79	6·4
			—	245	339		4·26	3·77		11·0
2,7-Dimethyl	8·80 ± 0·02		0	233	270	313	4·07	3·70	3·93	6·4
			—	245	331		4·29	3·86		11·0
2,6,7-Trimethyl	9·24 ± 0·06		0	233	267	316	4·06	3·81	3·91	6·5
			—	245	332		4·32	3·85		11·3
3-Aminopyrazine-2-carboxylic acid (II; Y = OH)										
No other substituent			—	243	340		4·03	3·76		7·0
6-Methyl			—	245	347		4·06	3·77		7·0
5-Methyl			—	246	342		4·01	3·87		7·0
5,6-Dimethyl			—	248	343		4·01	3·86		7·0
3-Aminopyrazine-2-carbohydrazide (II; Y = NH·NH₂)										
5,6-Dimethyl	1·38 ± 0·04	360	++	251	371		4·12	4·05		−2 [e]
	2·96 ± 0·02	335	+ [d]	253	361		4·07	3·94		2·2
			0	253	355		4·08	3·91		6·7
6-Methyl	1·13 ± 0·04	245	++	247	368		4·11	3·87		−2 [e]
	3·07 ± 0·07	335	+ [d]	250	361		4·06	3·81		2·0
			0	250	360		4·09	3·80		6·9
5-Methyl	1·28 ± 0·06	245	++	247	360		4·10	4·04		−2 [e]
	3·05 ± 0·06	335	+ [d]	251	353		4·02	3·94		2·1
			0	251	350		4·06	3·93		6·7
No other substituent	1·06 ± 0·03	243	++	243	357		4·10	3·90		−2 [e]
	3·10 ± 0·11 [f]	335	+ [d]	247	354		4·08	3·84		2·1
			0	248	352		4·06	3·82		6·9
4,5-Diamino-6-hydroxy-2-methylpyrimidine										
	3·68 ± 0·06									
	10·67 ± 0·02		0	214	283		4·01	3·94		6·5
			—	274			3·93			13·0

[a] By potentiometric titration,[18] except where an analytical wavelength is specified; in those cases, pK_a values were determined spectrophotometrically in 0·01M-buffers.[19] [b] 0 = Neutral molecule, + = cation, ++ = di-cation, — = anion. [c] See also ref. 14. [d] Also contains some di-cation and neutral molecule. [e] H_0 in sulphuric acid (M. A. Paul and F. A. Long, *Chem. Rev.*, 1957, **57**, 12). [f] Large spread due to small spectral change on ionisation.

1,2- or 2,3-bond first would lead to a 2-amino-3-carbamoylpyrazine (II; Y = NH_2), and amide exchange with hydrazine would be necessary to give the hydrazide actually isolated (see, however, ref. 9). No amide was detected during some of the reactions, and only a little during the others. Control experiments showed that conversion of amide into hydrazide was fairly slow under the reaction conditions used, and that as little as 3% of amide would have been readily detected in the presence of hydrazide, by thin-layer chromatography. Furthermore, it is now clear that, if a substantial part of the reaction did involve initial attack at the 2-position, the introduction of a 2-methyl group would slow pyrimidine ring-opening considerably without greatly affecting the rate of pyrazine cleavage. In fact, the proportion of pyrazine obtained from 4-hydroxy-2-methylpteridine was only a little less than that from 4-hydroxypteridine.

Plausible mechanisms for related pyrimidine ring-openings have already been suggested.[8,9,17]

EXPERIMENTAL

Ultraviolet spectra were measured on a Unicam S.P. 800 recording spectrophotometer, and $\lambda_{max.}$ and $\varepsilon_{max.}$ values were checked on a Unicam S.P. 500 manual instrument.

pK_a values were measured by potentiometric titration [18] using an E.I.L. model 38A pH-meter, or spectrophotometrically in 0·01M buffers.[19]

4-Hydroxy-2,6-dimethylpteridine.—2-Amino-3-carbamoyl-5-methylpyrazine [20] (1·0 g.), freshly distilled ethyl orthoacetate (20 ml.), and acetic anhydride (20 ml.) were heated under reflux (bath 120—125°) for 22 hr. The mixture yielded a solid (0·45 g.) on cooling, and a further 0·1 g. on partial evaporation. The combined solids were crystallised from ethanol (charcoal), to give the *product* (0·35 g.), m. p. >250° (Found: C, 54·1; H, 4·9; N, 32·0. $C_8H_8N_4O$ requires C, 54·5; H, 4·6; N, 31·8%).

4-Hydroxy-2,7-dimethylpteridine.—Methylglyoxal (2 ml. of 25% aqueous solution), 4,5-diamino-6-hydroxy-2-methylpyrimidine (1 g.), and water (30 ml.) were shaken and gently heated to give a clear solution which was kept for ½ hr., evaporated to dryness under reduced pressure, and the residue crystallised from ethanol (charcoal), to yield the *product* (0·5 g.), m. p. >250° (Found: C, 54·4; H, 4·85; N, 31·4%).

The compound was tested for contamination by the other possible reaction product, 4-hydroxy-2,6-dimethylpteridine, as follows. A little of the material was treated with boiling hydrazine hydrate for 1 hr., and the solution examined, after removal of the bulk of pyrazine hydrazide formed, by thin-layer chromatography on silica gel. No 4,5-diamino-6-hydroxy-2-methylpyrimidine could be detected, although this would have been the major product from any 2,6-dimethyl-isomer present (see Table 1).

Ring-opening of 4-Hydroxypteridines by Hydrazine.—(a) *Pteridines containing a 7-methyl group.* 4-Hydroxy-6,7-dimethylpteridine (1·0 g.) and 99% hydrazine hydrate (5 ml.) were heated on a boiling-water bath for 1½ hr. The cooled solution gave *3-amino-5,6-dimethylpyrazine-2-carbohydrazide* (0·8 g.) which crystallised from water as pale yellow needles, m. p. 209° (Found: C, 46·5; H, 6·2; N, 38·5. $C_7H_{11}N_5O$ requires C, 46·4; H, 6·1; N, 38·7%).

The 7-methyl-, 2,7-dimethyl-, and 2,6,7-trimethyl-derivatives of 4-hydroxypteridine similarly yielded the corresponding 3-aminopyrazine-2-carbohydrazides.

3-Amino-5-methylpyrazine-2-carbohydrazide had m. p. 190° (Found: C, 42·9; H, 5·5; N, 41·8. $C_6H_9N_5O$ requires C, 43·1; H, 5·4; N, 41·9%).

(b) *Pteridines without a 7-methyl group.* (i) 4-Hydroxypteridine (0·5 g.) and 99% hydrazine hydrate (2 ml.) were heated on a boiling-water bath for 1 hr. The solution was slowly cooled to 40°, when 3-aminopyrazine-2-carbohydrazide (0·04 g.), m. p. 206—208° (lit.,[21] 207—209°), separated. The filtrate was evaporated to dryness under reduced pressure, and the residue crystallised twice from water, to yield 4,5-diamino-6-hydroxypyrimidine (0·22 g.), m. p. 241° (lit.,[21] 243°). (ii*a*) 4-Hydroxy-6-methylpteridine (0·5 g.) and 99% hydrazine hydrate (2 ml.) were heated on a boiling-water bath for 1 hr. The solution was evaporated to dryness under reduced pressure, and the residue heated under reflux with acetone (15 ml.) for 1 hr. Filtration of the hot solution followed by crystallisation of the insoluble residue from water gave 4,5-diamino-6-hydroxypyrimidine (0·1 g.), m. p. 241°, identical with an authentic specimen. The acetone solution was evaporated to dryness, and the residue treated with water (10 ml.). The resulting solid was filtered off and twice crystallised from water, to yield the *isopropylidene derivative* of *3-amino-6-methylpyrazine-2-carbohydrazide* (0·08 g.), m. p. 178° (Found: C, 52·1; H, 6·7; N, 33·4. $C_9H_{10}N_5O$ requires C, 52·2; H, 6·3; N, 33·8%). 3-Amino-6-methylpyrazine-2-carbohydrazide itself was also isolated from a similar reaction, but less conveniently. (ii*b*) 4-Hydroxy-6-methylpteridine (0·2 g.) was heated with hydrazine hydrate (5 ml.) on a boiling-water bath for 4 hr., and the solution evaporated to dryness. Crystallisation from ethanol gave yellow *plates* (0·14 g.), m. p. 192—193°, identical with those obtained by crystallising together equimolecular proportions of 4,5-diamino-6-hydroxypyrimidine and 3-amino-6-methylpyrazine-2-carbohydrazide (synthesis below) (Found: C, 40·6; H, 5·1; N, 43·1. $C_4H_6N_4O,C_6H_9N_5O$ requires C, 41·0; H, 5·2; N, 43·0%). (iii) 4-Hydroxy-2,6-dimethylpteridine (0·2 g.) yielded 4,5-diamino-6-hydroxy-2-methylpyrimidine (0·09 g.) and the isopropylidene derivative of 3-amino-6-methylpyrazine-2-carbohydrazide (0·05 g.) when treated as described in (ii*a*) above. (iv) 4-Hydroxy-2-methylpteridine (0·1 g.) was heated with 99% hydrazine hydrate (0·5 ml.) on a boiling-water bath for 1 hr. The mixture was cooled to room temperature, diluted with a little water, and filtered. Crystallisation of the residue from water gave 4,5-diamino-6-hydroxy-2-methylpyrimidine (0·06 g.), identical with an authentic specimen.

All the above ring-opening reactions were also followed by thin-layer chromatography on silica gel, in order to identify minor reaction products. Solvent systems used were butanol–5N-acetic acid (2 : 1), methanol–benzene

[17] E. C. Taylor, jun., and C. K. Cain, *J. Amer. Chem. Soc.*, 1951, **73**, 4384.

[18] A. Albert and E. P. Serjeant, "Ionisation Constants of Acids and Bases," Methuen, London, 1962.

[19] D. D. Perrin, *Austral. J. Chem.*, 1963, **16**, 572.

[20] O. Vogl and E. C. Taylor, *J. Amer. Chem. Soc.*, 1959, **81**, 2473.

[21] A. Albert, D. J. Brown, and G. Cheeseman, *J. Chem. Soc.*, 1951, 482.

(1 : 4), dimethylformamide–chloroform (1 : 4), and propan-2-ol–ammonia (*d* 0·88)–water (20 : 1 : 2). Pyrimidines and pyrazines were detected in ultraviolet light (360 or 254 mμ) on plain or fluorescent silica gel plates, and hydrazones by spraying with 2,4-dinitrophenylhydrazine solution or in ultraviolet light (360 mμ).

The presence of the following substances, in addition to those isolated, was noted. (a) The dihydrazone of a dicarbonyl compound wherever a diaminopyrimidine was obtained (*e.g.*, methylglyoxal dihydrazone from 4-hydroxy-6-methylpteridine). (b) A little of the corresponding 2-amino-3-carbamoylpyrazine from ring-opening of 4-hydroxy-7-methyl-, 4-hydroxy-6,7-dimethyl- and (trace only) 4-hydroxy-2,7-dimethyl-pteridine. The ratio of amide to hydrazide formed in these reactions was shown to be less than 5%, even in the most favourable case, by the method described below (see amide-into-hydrazide conversion). (c) 3-Aminopyrazine-2-carbohydrazide in reaction (*iv*).

3-*Amino-6-methylpyrazine-2-carbohydrazide*.—A mixture of 3-amino-6-methylpyrazine-2-carboxylic acid (0·4 g.), methanol (1 ml.), and concentrated sulphuric acid (1 ml.) was kept for 66 hr. The solution was poured into 85% hydrazine hydrate (5 ml.), and the temperature was kept below 30° during the addition. The solid which separated was washed with water and crystallised from ethanol, to yield the yellow *product* (0·125 g.), which gradually melted above 140° (Found: C, 43·4; H, 5·6; N, 41·6. $C_6H_9N_5O$ requires C, 43·1; H, 5·4; N, 41·9%).

Conversion of Pyrazine Amides into Hydrazides.—The following is typical. 3-Amino-5-methylpyrazine-2-carboxyamide (0·01 g.) was heated on a water bath with hydrazine hydrate (0·1 ml.). Samples were spotted at intervals, on thin-layer plates coated with silica gel, and eluted with dimethylformamide–chloroform (1 : 10) or propan-2-ol–ammonia (*d* 0·88)–water (40 : 2 : 1). 3-Amino-5-methylpyrazine-2-carbohydrazide was detectable after a few minutes and present in 70% yield after 2½ hr. The extent of conversion at any time was estimated, approximately, by eluting a sample, removing separately the areas containing amide and hydrazide spots, and dissolving out the organic material from each with pH 7 phosphate buffer (5 ml.). The ratio of amide to hydrazide was calculated from the ultraviolet spectra of these solutions. A similar experiment was carried out using 3-amino-6-methylpyrazine-2-carboxyamide (0·1 g.), and the hydrazine removed by evaporation. Crystallisation of the residue from ethanol gave 3-amino-6-methylpyrazine-2-carbohydrazide (0·05 g.), identical with an authentic specimen.

Quantitative Ring-openings with Hydrazine.—Each pteridine (0·100 g.) was heated with 99% hydrazine hydrate (0·5 ml.) on a boiling-water bath for 1 hr., and the whole reaction mixture diluted to 1 l. with deionised water. A 5-ml. aliquot was diluted to 50 ml. with phosphate buffer so that the final pH was 7. The ultraviolet spectrum of the solution was analysed to obtain the quantities of reaction products indicated by the qualitative experiments described above (results in Table 1).

Ring-opening of 4-Hydroxypteridines by Alkali.—(a) *Compounds with no 2-methyl group*. As ref. 1.

(b) *Compounds with a 2-methyl group*. 2-Methyl-, 2,6- and 2,7-dimethyl-, and 2,6,7-trimethyl-4-hydroxypteridine were much more resistant to alkali. Hydrolysis proceeded faster in 2N- than in 10N-sodium hydroxide. Reaction times of 72 hr. upwards were required. The following reaction is typical. 4-Hydroxy-2-methylpteridine (0·10 g.) and 2N-sodium hydroxide (10 ml.) were heated under reflux in a Polythene-lined glass vessel for 86 hr. (bath 115°). The solution was evaporated to dryness, and the residue dissolved in warm water (3 ml.). When the pH of the solution was reduced to 2 (dilute H_2SO_4), 3-aminopyrazine-2-carboxylic acid (0·05 g.), m. p. 203°, separated. When the reaction was carried out in a Pyrex vessel, large quantities of silica were precipitated at this stage.

Quantitative Ring-openings in Alkali.—Each pteridine (0·01 g.) was heated under reflux (bath 120—130°) with 2N-sodium hydroxide (2·0 ml.) for 3—72 hr. The whole reaction mixture was partially neutralised with dilute hydrochloric acid and diluted to 100 ml. A 5-ml. aliquot was diluted and buffered, to give a volume of 50 ml. and pH 5·5. The ultraviolet spectrum of each solution was measured and the amount of pyrazinecarboxylic acid and unchanged pteridine (if any) calculated.

The authors thank Miss M. Bowling for technical assistance, and Mr. A. E. Cunliffe for measuring pK_a values. One of them (G. N.) thanks the Governors of the Royal College of Advanced Technology for the award of a Demonstratorship.

Department of Chemistry and Applied Chemistry,
Royal College of Advanced Technology,
Salford 5, Lancashire.

[6/001 *Received, January 3rd*, 1966]