Heterocyclic Studies. Part XI.[1] Some 3-Methoxypteridin-4(3*H*)-ones

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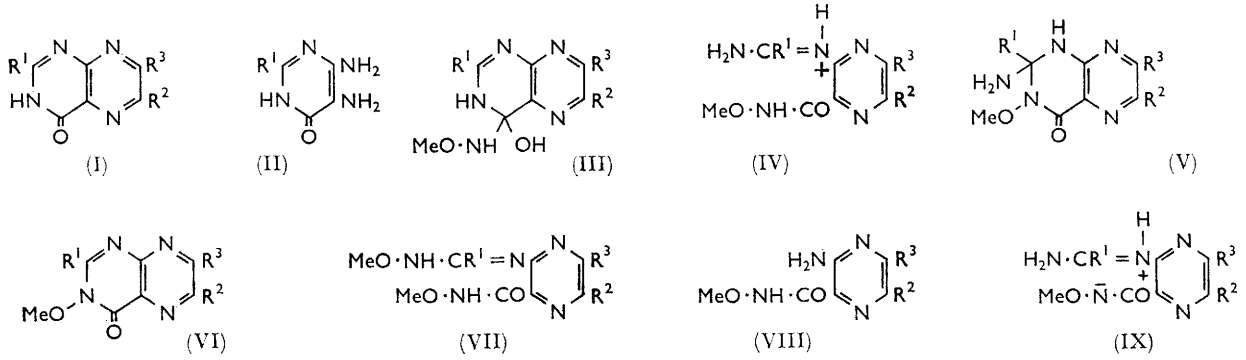
Treatment of pteridin-4(3*H*)-one (Ia) with aqueous methoxyamine solution at 70° and pH 6 gave 85% of 4,5-diaminopyrimidin-6(1*H*)-one (IIa) but at pH 7·5 gave none of the pyrimidine and 46% of methyl 3-(methoxyiminomethylamino)pyrazine-2-carbohydroxamate (VIIa). 6-Methylpteridin-4(3*H*)-one behaved similarly.

Cyclisation of the pyrazine (VIIa), its 5- and 6-methyl- and its 5,6-dimethyl-derivatives (VIIb–d) gave 3-methoxypteridin-4(3*H*)-ones (VIa–d). These pteridines were also prepared by treating methyl 3-aminopyrazine-2-hydroxamates (VIIIa–d) with formic acid and acetic anhydride. Treatment of methyl 3-aminopyrazine-2-hydroxamates (VIIIa and d) with acetic acid and acetic anhydride gave 3-methoxy-2-methylpteridin-4(3*H*)-ones (VIe and f). The *N*-methoxypteridines were very readily cleaved by methoxyamine.

^{1}H N.m.r. spectra are recorded and the mechanisms of the ring-cleavage reactions are discussed.

Part VII of this series [2] described how some pteridin-4(3*H*)-ones (I) were cleaved with methoxyamine at pH 6 to yield various products including some methyl 3-(methoxyiminomethylamino)pyrazine-2-carbohydroxamates (VIIa—c). It was suggested [2] that the latter compounds arose from cleavage of the pteridines (Ia—c) to give amidines (IVa—c) which recyclised to give 3-methoxypteridin-4(3*H*)-ones (VIa—c). These, in turn, were considered to be cleaved by methoxyamine to the final products (VIIa—c). Since the intermediates (IV) and (VI) were not isolated and no 3-methoxypteridin-4(3*H*)-ones were known, it seemed desirable to synthesise and study some of the latter compounds in order to substantiate the validity of the reaction scheme outlined.



(I) (II) (III) (IV) (V) (VI) (VII) (VIII) (IX)

a; $R^1 = R^2 = R^3 = H$ c; $R^1 = R^2 = H$, $R^3 = Me$ e; $R^1 = Me$, $R^2 = R^3 = H$
b; $R^1 = R^3 = H$, $R^2 = Me$ d; $R^1 = H$, $R^2 = R^3 = Me$ f; $R^1 = R^2 = R^3 = Me$

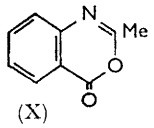
Compounds analogous to the desired 3-methoxypteridin-4(3*H*)-ones, *e.g.* 3-alkoxyquinazolin-4(3*H*)-ones, have been made by treating compounds containing an oxazinone ring with alkylhydroxylamines [*e.g.* (X) gave (XI)] [3,4] by alkylation of 3-hydroxyquinazolin-4(3*H*)-ones,[5] and by treatment of *o*-aminohydroxamates [*e.g.* (XII)] with formic acid or acetic anhydride.[3] However, the pyrazine derivatives (VII) which had already been prepared seemed likely intermediates for the synthesis of 3-methoxypteridin-4(3*H*)-ones and these were investigated first.

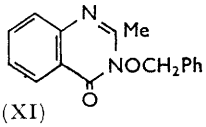
Only 7-methylpteridin-4(3*H*)-one (Ic) had given a useful yield of a suitable pyrazine (VIIc) [2] at pH 6 but it is now shown that with other pteridin-4(3*H*)-ones (Ia and b) the relative yields of various cleavage products are highly dependent on the pH at which reactions with methoxyamine are carried out. For example, pteridin-4(3*H*)-one (Ia) and 2M-methoxyamine at 70° and pH 6 gave 85% of 4,5-diaminopyrimidin-6(1*H*)-one (IIa) and at pH 6·5 gave none of the pyrimidine but 36% of a pyrazine (VIIa). The products varied over a wider pH range as indicated in Table 1. 6-Methylpteridin-4(3*H*)-one (Ib) behaved similarly so that by suitable choice of reaction conditions two more of the desired pyrazines (VIIa and b) now became available in reasonable yield. Since pteridin-4(3*H*)-ones containing a 7-methyl group do not undergo pyrazine ring-cleavage with methoxyamine [2] or other nucleophiles [6] a rise in the pH of the reaction mixture had no effect on the pattern of products from such compounds except that the decomposition of the reagent and primary reaction products was accelerated.

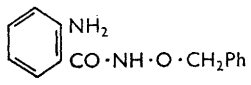
The pH dependence of the products of ring-cleavage

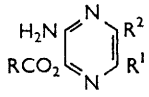
[1] Part X, J. Clark and P. N. T. Murdoch, *J. Chem. Soc.* (*C*), 1969, 1883.
[2] J. Clark, G. Neath, and C. Smith, *J. Chem. Soc.* (*C*), 1969, 1297.
[3] P. Mamalis, M. J. Rix, and A. A. Sarsfield, *J. Chem. Soc.*, 1965, 6278.
[4] H. Taniyama, B. Yasiu, H. Uchida, and Y. Okuda, *J. Pharm. Soc. Japan*, 1961, **81**, 431.
[5] S. Somasekhara, V. S. Dighe, P. V. Arur, and S. L. Mukherjee, *Current Sci.*, 1964, **33**, 746.
[6] (*a*) J. Clark and G. Neath, *J. Chem. Soc.* (*C*), 1966, 1112; (*b*) *ibid.*, 1968, 919.

arises because the postulated intermediate amidine (IVa or b) can cyclise in two ways. Attack by the nitrogen atom of the hydroxamate group of (IV) on the


(X)


(XI)


(XII)


(XIII)

CH of its amidine side-chain gives (V) and hence, by loss of ammonia, the *N*-methoxypteridine (VI). Further reaction of the latter with methoxyamine leads to the pyrazine (VII) which was isolated. Alternatively, attack by the terminal amino-group of the amidine side-chain of (IV) on the hydroxamate carbonyl carbon atom gives (III) which loses methoxyamine to give the pteridin-4(3*H*)-one (I). The latter reaction simply reverses the original ring-opening step, maintaining the concentration of pteridin-4(3*H*)-one, and enabling the possibly much slower but irreversible pyrazine-ring opening to give a high yield of 4,5-diaminopyrimidin-6(1*H*)-one (IIa) under suitable conditions. The balance between the alternative cyclisations of (IV) changes at pH values higher than 6 due to ionisation of the hydroxamate group as an anion. The now more nucleophilic hydroxamate nitrogen atom of (IX) favours cyclisation leading to the *N*-methoxypteridine (VI) and thence to the product actually isolated (VII). At the same time cyclisation to the pteridin-4(3*H*)-one (I) is discouraged by the reduced polarisation of the carbonyl group. 3-Hydroxypteridin-4(3*H*)-ones analogous to (VI) were obtained during similar ring-openings with hydroxylamine but they were stable to further attack by the reagent and hence could be isolated.[6b]

The above argument hinges on the ionisation constants of the intermediate amidines (IV) but since the compounds cannot be isolated the pK_a values cannot be measured. However, the amidine side-chain can be assumed to be ionised as a cation (IV) at least at the lower pH values used. Acetamidine, a typical amidine, has a pK_a value of *ca.* 12·3,[7] and although electron-deficient aromatic systems directly attached to the nitrogen atoms of amidines reduce their pK_a values the effect is not very pronounced.[8] The pK_a values for the hydroxamate groups of the amidines (IV) should be *ca.* 7—8 by analogy with aromatic hydroxamic acids.[9] Furthermore, they must be very similar [10] to those of the closely related pyrazines (VII) the pK_a values of which can be measured. Methyl 3-(methoxyiminomethylamino)pyrazine-2-carbohydroxamate (VIIa) has a pK_a value for ionisation of the methoxycarbamoyl group of *ca.* 7·2 at 20° which suggests that the similar group of the corresponding amidine (IVa) would start to become appreciably ionised close to pH 6, the value at which the product pattern begins to change. The rapid increase in the yield of pyrazine with increase of pH is soon offset by the lack of stability of both reagent and products at higher pH values and possibly also by slower cyclisation as deprotonation of the amidinium side-chain becomes appreciable at the highest pH values used. Water soluble by-products which are probably pyrazine derivatives with a carboxylic acid group were the major products above pH 8·5.

None of the pyrazine (VIIe) was produced by the reaction of 2-methylpteridin-4(3*H*)-one (Ie) with methoxyamine, presumably because the methyl group hinders cyclisation of the amidine (IXe) to the methoxy-

TABLE 1

Ring-opening of pteridin-4(3*H*)-ones with methoxyamine *

Pteridin-4-(3*H*)-one			Reaction conditions				Products and yields (%)		
R[1]	R[2]	R[3]	Reagent concn.*	pH	Time (hr.)	Temp.	Pyrimidine (II) †	Pyrazine (VIII) †	Pyrazine (VII) †
H	H	H	2M	6·0	24	70—75°	81		11
H	H	H	2M	6·5	24	70—75			36
H	H	H	2M	7·0	24	70—75			41
H	H	H	2M	7·5	24	70—75			46
H	H	H	2M	8·0	24	70—75			37
H	H	H	2M	8·5	24	70—75			38
H	H	H	2M	9·0	24	70—75			28
Me	H	H	2M	6·0	24	70—75	75		
H	Me	H	2M	6·0	24	70—75	83		7
H	Me	H	2M	7·5	100	70—75			27
H	H	Me	2M	6·0	48	70—75			50
H	H	Me	2M	7·5	100	70—75			26
H	Me	Me	4M	6·0	24	100		35	
H	Me	Me	4M	7·5	24	100			20
Me	H	Me	4M	6·0	24	100		32	

* See Experimental section. † Substituents as appropriate to starting material in column 1.

[7] G. Schwarzenbach and K. Lutz, *Helv. Chim. Acta*, 1940, **23**, 1162; J. C. Gage, *J. Chem. Soc.*, 1949, 221.
[8] E. Lorz and R. Baltzly, *J. Amer. Chem. Soc.*, 1949, **71**, 3992.
[9] R. L. Dutta and S. Ghosh, *J. Indian Chem. Soc.*, 1967, **44**, 820; F. Baroncelli and G. Grossi, *J. Inorg. and Nuclear Chem.*, 1965, **27**, 1085.
[10] J. Clark and D. D. Perrin, *Quart. Rev.*, 1964, **18**, 295.

pteridine (VIe). Degradation of (IXe) to water soluble by-products therefore ensues.

As expected, methyl 3-(methoxyiminomethylamino)-pyrazine-2-carbohydroxamates (VIIa—d) were readily converted into the desired 3-methoxypteridin-4(3*H*)-ones (VIa—d). The pyrazines when heated in buffered aqueous solution of pH value 3·8 underwent ready cyclisation to give good yields of product.

The above route from pteridin-4(3*H*)-ones to 3-methoxypteridin-4(3*H*)-ones was only convenient when the parent pteridin-4(3*H*)-ones (I) were readily cleaved by methoxyamine. This was not the case with di- or trimethyl derivatives. At the higher temperature required for ring cleavage of these compounds [2] the desired products (VII) were gradually degraded to methyl 3-aminopyrazine-2-hydroxamates (VIII) and other pyrazines. Decomposition of the reagent, particularly at higher pH values, also led to side-reactions. Methyl 3-aminopyrazine-2-hydroxamates (VIII) were therefore considered as alternative precursors of 3-methoxypteridin-4(3*H*)-ones (VI).

In the present work it was convenient to make these pyrazines (VIIIa—d) by the higher temperature ring-cleavage of pteridin-4(3*H*)-ones (Ia—d) with methoxyamine or by degrading the pyrazines (VIIa—d) with acetate buffer at 100°. Normally they may be better obtained from esters of 2-aminopyrazine-3-carboxylic acids (XIII; R = Me or Et). Treatment of the methyl 3-aminopyrazine-2-hydroxamates (VIIIa, c, or d) with formic acid and acetic anhydride or ethyl orthoformate and acetic anhydride readily gave 3-methoxypteridin-4(3*H*)-ones (VIa, c, d). 2-Methyl derivatives (VIe and f) were similarly prepared by treating the amino-pyrazines (VIIIa and d) with acetic acid and acetic anhydride.

Structures of the 3-methoxypteridin-4(3*H*)-ones were established by ^{1}H n.m.r. spectroscopy which clearly showed the presence both of two aromatic rings and the N–OMe group in each compound (see Table 2). As predicted the compounds (VI) were very readily reconverted into methyl 3-(methoxyiminomethylamino)pyrazine-2-carbohydroxamates (VII) by methoxyamine. This supports the reaction schemes postulated above and previously.[2] The two types of compound [(VI) and (VII)] may well be in mobile equilibrium in methoxyamine solution.

EXPERIMENTAL

Ring-opening with Methoxyamine.—The reagent used was an aqueous solution of methoxyamine hydrochloride adjusted to the required concentration and pH value (Table 1) by the addition of aqueous sodium hydroxide.

The pteridin-4(3*H*)-one (Ia—d) (0·5 g.) and methoxyamine solution (10 ml.) were heated at the required temperature for the required time (see Table 1). The pH value of the cooled solution was adjusted to 4 before it was evaporated to dryness under reduced pressure. The residue was dried over concentrated sulphuric acid and was continuously extracted with benzene. The benzene solution yielded the pyrazine derivative [(VII) or (VIII)] which was crystallised from, benzene–light petroleum (b.p. 60—80°). The benzene-insoluble residue was extracted with ethanol to obtain any 4,5-diaminopyrimidine-6(1*H*)-one or its 2-methyl derivative which was formed. Products from individual reactions are detailed in Table 1.

Degradation of Methyl 3-(Methoxyiminomethylamino)-pyrazine-2-carbohydroxamates (VII).—The pyrazine derivative (VIIa or c) (0·3 g.), glacial acetic acid (10 ml.), water (10 ml.), and sodium acetate (4 g.) were heated at 100° for 5 hr. The solution was evaporated to dryness and the residue was continuously extracted with benzene. Removal of the solvent and crystallisation of the product from benzene–light petroleum (b.p. 60—80°) gave, as appropriate, *methyl 3-aminopyrazine-2-hydroxamate* (VIIIa) (0·18 g.), m.p. 129° (Found: C, 42·7; H, 4·8; *M* (mass spectrum), 168. $C_6H_8N_4O_2$ requires C, 42·8; H, 4·8%; *M*, 168), or the 5-methyl derivative (VIIIc) (0·14 g.) identical with that described previously.[2]

3-*Methoxypteridin*-4(3H)-*ones* (VI).—(*a*) The methyl 3-(methoxyiminomethylamino)pyrazine-2-carbohydroxamate (VIIa, b, c, or d) (0·025 g.) and succinate buffer solution [0·1M-succinic acid (1 ml.), 0·1M-potassium hydroxide solution (0·3 ml.), and water (1·7 ml.) giving pH 3·8] were heated at 80° for 3½ hr. The resulting solution was continuously extracted with chloroform. The extract was dried with sodium sulphate and the solvent was removed under reduced pressure to yield the *pteridinone* (VIa, b, c, or d) which was crystallised from a suitable solvent (see Table 3).

(*b*) The methyl 3-aminopyrazine-2-hydroxamate (VIIIa,

TABLE 2

^{1}H N.m.r. spectra *

Compound	Chemical shifts (τ) of stated groups: *C*-Methyl (s)	*O*-Methyl	Aromatic protons: 2-H	7- and 6-H's		NH_2	NH
(VIII; $R^2 = R^3 = H$)		6·07		2·22 †‡	1·79 †‡	3·30	−0·22
(VI; $R^1 = R^2 = R^3 = H$)		5·72	1·37	1·07 †	0·93 †		
(VI; R^1 = Me, $R^2 = R^3 = H$)	7·22	5·78		1·16 †	1·00 †		
(VI; R^2 = Me, $R^1 = R^3 = H$)	7·15	5·74	1·42		1·06		
(VI; $R^1 = R^2 = H$, R^3 = Me)	7·18	5·73	1·38	1·20			
(VI; $R^1 = H$, $R^2 = R^3$ = Me)	7·22 (6H)	5·75		1·45			
(VI; $R^1 = R^2 = R^3$ = Me)	7·20 (6H) 7·25 (3H)	5·75					

* Using a Varian A60A spectrometer with $CDCl_3$ as solvent and tetramethylsilane as internal standard. † Doublet, *J* 2·5 Hz. ‡ Pyrazine proton.

TABLE 3

3-Methoxypteridin-4(3*H*)-one (VI)			Method of Prepn.*	Yield (%)	M.p.	Crysn. solvent ‡	Found			Required		
R^1	R^2	R^3					C	H	*M* †	C	H	*M*
H	H	H	a	74	197°	E	47·7	3·5	178	47·2	3·4	178
H	H	H	b	71	197	E						
Me	H	H	c	44	183	P	50·2	4·4	192	50·0	4·2	192
H	Me	H	a	55	215—217	E	49·5	4·2	192	50·0	4·2	192
H	H	Me	a	62	214—215	E	49·5	4·0	192	50·0	4·0	192
H	H	Me	b	48	214—215	E						
H	Me	Me	a	50	145	LP	52·9	5·0	206	52·4	4·9	206
H	Me	Me	b	60	145	LP						
Me	Me	Me	c	56	166—167	CT	54·1	5·7	220	54·6	5·5	220

* See Experimental section. † Mass spectrum. ‡ E = ethanol, P = propan-2-ol, LP = light petroleum (b.p. 80—100°), CT = carbon tetrachloride.

c, or d) (0·1 g.), formic acid (1·7 ml.), and acetic anhydride (1·2 ml.) were heated at 80° for 1½ hr. The resulting solution was poured into water and the product (VIa, c, or d) was extracted with chloroform (see Table 3).

(*c*) The methyl 3-aminopyrazine-2-hydroxamate (0·1 g.) (VIIIa or c), glacial acetic acid (1 ml.), and acetic anhydride (1 ml.) were heated at 100° for 2½ hr. The resulting solution was poured into water and the *product* (VIe or f) was extracted with chloroform.

Ring-cleavage of 3-methoxypteridin-4(3H)*-ones.*—The pteridine (VIa or c) (0·04 g.) and 2M-methoxyamine solution (2·0 ml., pH 6), were heated at 70° for 10 min. The solution was evaporated to dryness and the residue was extracted with benzene to yield the appropriate methyl 3-(methoxyiminomethylamino)pyrazine-2-carbohydroxamate (VIIa or c) (0·03 g.), identical with specimens described above.

The authors thank Mr. D. Barraclough and Mr. B. Marquis who measured the n.m.r. spectra, and Mrs. Ruth Maynard who measured the mass spectra on an AEI MS12 mass spectrometer.

[9/654 *Received, April 23rd,* 1969]