Heterocyclic Studies. Part XXVI.[1] Cleavage of Pyrimido[5,4-*e*]-*as*-triazin-5(6*H*)-one by Nucleophiles

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Pyrimido[5,4-*e*]-*as*-triazin-5(6*H*)-one was readily cleaved by morpholine or 1,1-dimethylhydrazine to yield 6-amino-5-morpholinocarbonyl-*as*-triazine or the corresponding 5-*NN*-dimethylcarbohydrazide. The pyrimidotriazinone and hydroxylamine gave 6-hydroxypyrimido[5,4-*e*]-*as*-triazin-5(6*H*)-one, whereas the pyrimidotriazinone and methoxyamine gave methyl 6-(methoxyaminomethyleneamino)-*as*-triazine-5-carbohydroxamate.

RING cleavage of pteridin-4(3*H*)-one (I) and its derivatives by simple nucleophiles such as hydroxide ion [2,3] or amines [4] invariably occurred in the pyrimidine ring, following initial attack at the 4- or 2-position. In contrast, nucleophiles containing an amino-group next to an electronegative atom were capable of opening either ring of pteridin-4(3*H*)-one.[2,5-7] It was suggested that pyrazine ring opening involved preliminary addition of one molecule of reagent to give an intermediate [*e.g.* (II)] which suffered attack at the 6-position by a further molecule of reagent.[6]

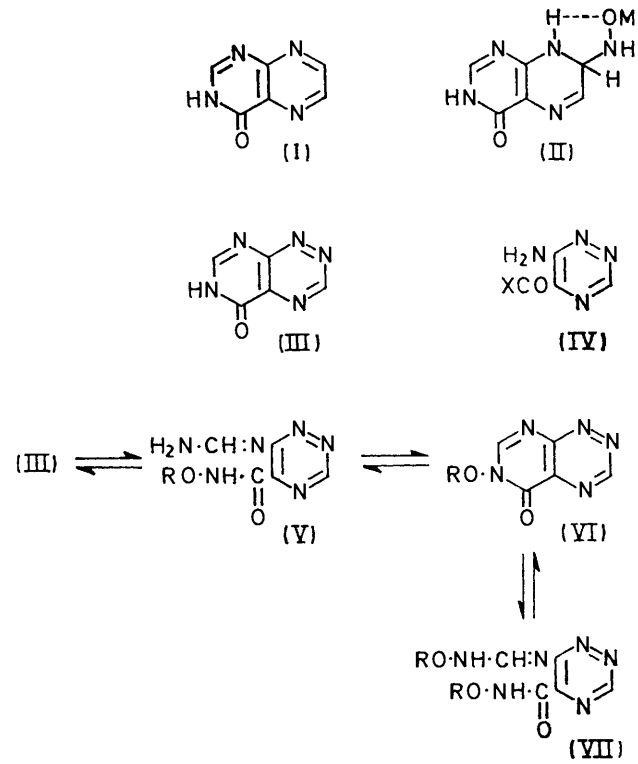
We now report some ring-opening reactions of pyrimido[5,4-*e*]-*as*-triazin-5(6*H*)-one (III),[8] which is a close analogue of pteridin-4(3*H*)-one but lacks the pair of adjacent polarised C=N linkages which permit the special ring-opening mechanism which operates in the pteridine.

Ready pyrimidine-ring cleavage of the pyrimidotriazinone (III) had previously been indicated by its conversion into 6-amino-*as*-triazine-5-carboxamide (IV; X = NH_2) on treatment with aqueous ethanolic triethylamine,[8] and was now confirmed by treatment with morpholine in ethanol which yielded the expected substituted amide (IV; X = morpholino). Use of neat morpholine quickly gave a tar which could not be purified.

Treatment of the pyrimidotriazinone (III) with hydrazine hydrate or methylhydrazine, under a variety of conditions, gave only intractable tars. These reactions probably went *via* the carbohydrazides (IV; X = $NH{\cdot}NH_2$ or NH·NHMe) since the less reactive 1,1-dimethylhydrazine gave a dimethylcarbohydrazide (IV; X = $NH{\cdot}NMe_2$) in good yield.

Pyrimido[5,4-*e*]-*as*-triazin-5(6*H*)-one (III) and hydroxylamine at pH 6 gave 6-hydroxypyrimido[5,4-*e*]-*as*-triazin-5(6*H*)-one (VI; R = H) as the only product, and this was presumably [5] formed by recyclisation of the intermediate (V; R = H) which resulted from an initial cleavage reaction.

The pyrimidotriazinone (III) and methoxyamine gave a product (VII; R = Me), which was analogous to those obtained from pteridin-4(3*H*)-ones,[6] by a ring cleavage, cyclisation, and second ring-cleavage sequence [(III) ⟶ (V) ⟶ (VI) ⟶ (VII; R = Me)]. Attempts to recyclise the dimethoxy-compound (VII; R = Me) resulted in its degradation to a triazinecarbohydroxamate (IV; X = NH·OMe).



Reaction conditions necessary for nucleophilic cleavage of the pyrimidotriazinone (III) were consistently milder than those required for the corresponding pteridinone (I), as expected from its higher nitrogen to carbon ratio,[9] but no product from cleavage of the triazine ring was observed in any reaction. The latter result was in agreement with the absence of the special structural features claimed [6] to permit pyrazine ring opening by such reagents as hydrazine.

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

Compound	Solvent	Chemical shifts (τ) and assignments: Triazine proton	Other CH's	OMe or NMe	Exchangeable protons
(IV; X = NH·NMe$_2$)	$CDCl_3$	0·85		7·25 (6H)	1·33
(IV; X = morpholino)	$CDCl_3$	0·78	6·15 (8H, m) †		3·93
(IV; X = NH·OMe)	$CDCl_3$	0·85		6·07 (3H)	
(VII; R = Me)	$CDCl_3$	0·65	1·65 ‡	5·98 (3H) 6·03 (3H)	−0·37
(VI; R = H)	$(CD_3)_2SO$	0·62	1·28		

* Measured on a Varian A60A spectrometer at normal probe temperature with tetramethylsilane as internal standard. † Morpholine ring protons. ‡ Doublet, J 9 Hz, collapsed to singlet on deuteriation.

EXPERIMENTAL

6-*Amino*-5-*morpholinocarbonyl*-as-*triazine* (IV; X = morpholino).—A mixture of pyrimido[5,4-*e*]-*as*-triazin-5(6*H*)-one (0·2 g), ethanol (10 ml), and morpholine (0·4 ml) was heated under reflux for 48 h, then evaporated to dryness under reduced pressure. The residue was crystallised from light petroleum (b.p. 80—100°) to yield the yellow *amide* (0·08 g), m.p. 165° (Found: C, 46·0; H, 5·2; N, 33·2. $C_8H_{11}N_5O_2$ requires C, 45·9; H, 5·3; N, 33·5%).

6-*Amino*-as-*triazine*-5-(NN-*dimethyl*)*carbohydrazide* (IV; X = NH·NMe$_2$).— Pyrimido[5,4-e]-*as*-triazin-5(6*H*)-one (0·2 g) and freshly distilled 1,1-dimethylhydrazine (1 ml) were heated under reflux for 2½ h. The solution was evaporated to dryness and the residue extracted with boiling light petroleum (b.p. 80—100°). The cooled extract yielded the *dimethylcarbohydrazide* (0·16 g), m.p. 150—152° (Found: C, 39·5; H, 5·3; N, 46·5. $C_6H_{10}N_6O$ requires C, 39·5; H, 5·5; N, 46·1%).

6-*Hydroxypyrimido*[5,4-e]-as-*triazin*-5(6H)-*one* (VI; R = H).—Pyrimido[5,4-*e*]-*as*-triazin-5(6*H*)-one (0·2 g) and aqueous 2M-hydroxylamine (10 ml), adjusted to pH 6, were stirred at 20° for 2½ h. The pH value of the solution was adjusted to 3 with dilute hydrochloric acid before the solution was evaporated to dryness under reduced pressure. The residue was continuously extracted with chloroform and the volume of the extract was then reduced to yield the N-*hydroxy-compound* (0·1 g), m.p. 300° (charred) [Found: C, 36·2; H, 2·0%; M^+ (mass spectrum), 165. $C_5H_3N_5O_2$ requires C, 36·4; H, 1·8%; M, 165].

Methyl 6-(*Methoxyaminomethyleneamino*)-as-*triazine*-5-*carbohydroxamate* (VII; R = Me).—Pyrimido[5,4-*e*]-*as*-triazin-5(6*H*)-one (0·2 g) and aqueous 2M-methoxyamine (10 ml), adjusted to pH 6, were stirred at 20° for 3 h. The precipitated solid was crystallised from light petroleum (b.p. 80—100°) to yield the *ester* (0·18 g), m.p. 168—170° (Found: C, 37·7; H, 4·5; N, 36·8. $C_7H_{10}N_6O_3$ requires C, 37·2; H, 4·5; N, 37·15%).

Methyl 6-*Amino*-as-*triazine*-5-*carbohydroxamate* (IV; X = NH·OMe).—Methyl 6-(methoxyaminomethyleneamino)-*as*-triazine-5-carbohydroxamate (0·2 g), glacial acetic acid (5 ml), water (5 ml), and anhydrous sodium acetate (2 g) were heated on a boiling water-bath for 3½ h. The solution was evaporated to dryness under reduced pressure and the residue continuously extracted with light petroleum (b.p. 80—100°). The volume of the extract was reduced to yield the *ester* (0·09 g), m.p. 203—206° [Found: C, 35·3; H, 4·0%; M^+ (mass spectrum), 169. $C_5H_7N_5O_2$ requires C, 35·5; H, 4·2%; M, 169].

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