Pyrimidotriazine Studies. Part I. Ethyl 7-Chloropyrimido[5,4-*e*]-*as*-triazine-5-carboxylate and Related Compounds

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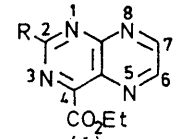
A route to ethyl 7-chloropyrimido[5,4-*e*]-*as*-triazine-5-carboxylate and its 1,2-dihydro-derivative is described, and the reactions of the former compound with amines are reported. The covalent hydration of the pyrimidotriazines is discussed.

ETHYL PTERIDINE-4-CARBOXYLATE (I; R = H) forms a stable isolable dihydrate (II; R = H) on treatment with water.[1] The pteridine is almost completely hydrated across the 5,6- and 7,8-bonds at equilibrium in aqueous solution. However, 4-trifluoromethylpteridine (III; R = H), which also bears a strong electron-withdrawing 4-substituent, adds water across the 3,4-bond in neutral aqueous solution to form the adduct (IV; R = H).[2] The presence of a 2-chloro-substituent favours the addition of water,[3,4] and replacement of a carbon atom by another nitrogen atom in the pyrazine ring, as in the pyrimidotriazine (V), further encourages addition at the



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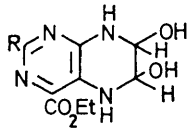

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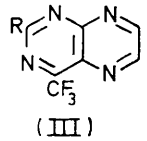

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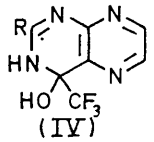

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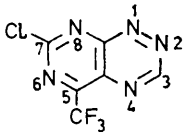

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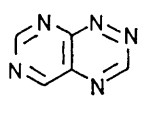
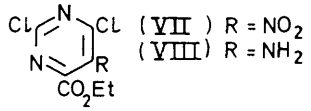


(VI)

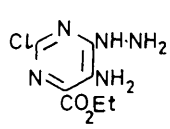
same position.[5] We hoped to establish whether the difference in hydration behaviour between ethyl pteridine-4-carboxylate and 4-trifluoromethylpteridine derivatives was parallelled in analogous pyrimidotriazines. 7-Aza-analogues of 4-trifluoromethylpteridine are known;[5] the compounds described here are 7-aza-analogues of some ethyl pteridine-4-carboxylates (I; R = Cl or NMe_2).

Extensive work has been carried out on the synthesis of biologically active pyrimido[5,4-*e*]-*as*-triazines, particularly fervenulin,[6] toxoflavin[7] (or xanthothricin[8]), and their analogues.[9,10] Recently the parent heterocycle (VI) and some methyl derivatives were prepared and shown to undergo addition at the 5,6-bond.[11] Introduction of 5-substituents in pyrimido[5,4-*e*]-*as*-triazines has been achieved *via* 5,6-adducts.[12,13]

Replacement of the 6-chlorine atom of ethyl 2,6-dichloro-5-nitropyrimidine-4-carboxylate (VII) with hydrazine was complicated by the presence of the ester carbonyl group, which also suffered nucleophilic attack. Hydrazinolysis of ester groups is known to occur,[14] and the presence of the nitro-group favours this reaction.[15] We therefore reduced the nitro-group and treated the resulting 5-amino-compound (VIII) with hydrazine. Even when the reaction was carried out at 4°, the product showed several spots on t.l.c., but the hydrazino-derivative (IX) precipitated from the reaction mixture in good yield. Treatment of compound (IX) with triethyl orthoformate and hydrochloric acid gave the expected chlorodihydropyrimidotriazine (X), which was oxidised with 1-chlorobenzotriazole[16] to the purple fully heteroaromatic compound (XI; R = Cl). The rate of addition of 1-chlorobenzotriazole was critical in this reaction; a red solution, probably containing 7-(benzotriazol-1-yl)pyrimido[5,4-*e*]-*as*-triazine-5-carboxylate (XI; R = benzotriazol-1-yl), resulted if addition was too rapid. Synthesis of this red compound was attempted by rapid addition of an excess of 1-chlorobenzotriazole followed by solvent extraction or preparative t.l.c. Neither procedure proved successful. Replacement of the chlorine atom of the heteroaromatic



(VII) R = NO_2
(VIII) R = NH_2



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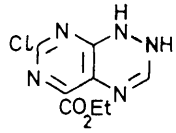
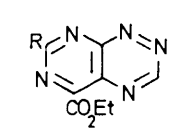


(X)



(XI)

compound (XI; R = Cl) with amines in anhydrous solvents occurred almost instantaneously at room temperature to give the products (XI; R = NMe_2 or $N[CH_2]_5$). Similar reactions were attempted with the chlorodihydro-compound (X) under more extreme conditions in

[1] J. Clark, *J. Chem. Soc.* (*C*), 1967, 1543.
[2] J. Clark and W. Pendergast, *J. Chem. Soc.* (*C*), 1969, 1751.
[3] J. Clark and W. Pendergast, *J. Chem. Soc.* (*C*), 1968, 1124.
[4] J. Clark and F. S. Yates, *J. Chem. Soc.* (*C*), 1971, 2278.
[5] J. Clark and F. S. Yates, *J. Chem. Soc.* (*C*), 1971, 2475.
[6] G. D. Davies, jun., R. K. Robins, and C. C. Cheng, *J. Org. Chem.*, 1961, 26, 5256; W. Pfleiderer and K. H. Schündehütte, *Annalen*, 1958, **615**, 42.
[7] G. D. Davies, jun., R. K. Robins, and C. C. Cheng, *J. Amer. Chem. Soc.*, 1961, **83**, 3904.
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[10] C. Temple C. L. Kussher and J. Montgomery, *J. Heterocyclic Chem.*, 1868, **5**, 581.
[11] M. E. C. Biffin, D. J. Brown, and T. Sugimoto, *J. Chem. Soc.* (*C*), 1970, 139.
[12] D. J. Brown and T. Sugimoto, *J. Chem. Soc.* (*C*), 1971, 2616.
[13] D. J. Brown and T. Sugimoto, *J.C.S. Perkin I*, 1972, 237.
[14] P. A. S. Smith, *Org. Synth.*, Coll. Vol. IV, 1963, p. 819.
[15] D. J. Brown, 'The Pyrimidines,' Wiley, New York, 1962, p. 8.
[16] C. W. Rees and R. C. Storr, *J. Chem. Soc.* (*C*), 1969, 1474.

alcoholic solution, but inseparable mixtures of starting material, the desired product, and other compounds, possibly 5,6-adducts (XII) were obtained. However, compound (X) yielded the 7-dimethylaminopyrimido-[5,4-*e*]-*as*-triazine (XI; R = NMe_2) on heating in dimethylformamide. Buncel and Symons reported that aqueous dimethylformamide yields dimethylamine on heating.[17]

All the pyrimidotriazines were highly coloured and showed some absorption in the visible region as well as in the u.v. Their structures were established by microanalysis and ^1H n.m.r. and mass spectroscopy. The n.m.r. spectra showed a low-field signal (Table 1) for the 3-proton of each of the aromatic compounds, confirming the presence of a fully aromatic triazine ring. The mass spectra showed molecular ions, which underwent stepwise losses of 28, 28, and 27 mass units, probably corresponding to loss of ethylene from the ester group and cleavage of the triazine ring involving loss of nitrogen and hydrogen cyanide. Similar fragmentation of the triazine ring has been observed in 5-trifluoromethylpyrimidotriazine derivatives.[18]

TABLE 1

^1H N.m.r. spectra [a]

Compound	Solvent	Chemical shifts (τ) [b] Ester CH_3 [c]	Ester CH_2 [d]	3-H	7-Subst.
(X) [e]	$(CD_3)_2SO$	8·72	5·65	3·40 [f]	
(XI; R = Cl)	$CDCl_3$	8·50	5·33	−0·37	
(XI; R = NMe_2)	$CDCl_3$	8·53	5·38	0·17	6·50
(XI; R = $N[CH_2]_2$)	$CDCl_3$	8·53	5·40	0·22	5·90,[g] 8·27 [g]
(XI; R = Cl)	$(CD_3)_2CO$	8·57	5·42	−0·42	
	$(CD_3)_2CO$–D_2O	8·77 [h]	5·72 [h]	0·57 [h]	

[a] Measured on a Varian T60 spectrometer, at normal probe temperature, with tetramethylsilane as internal standard. [b] Signals are singlets unless stated otherwise. [c] t, *J* 8 Hz. [d] q, *J* 8 Hz. [e] Exchangeable H at τ −0·15 and 1·22. [f] d, *J* 4 Hz. Coupling illustrated by deuteriation when signal at τ 3·40 (3-H) collapsed to a singlet. [g] m. [h] 5,6-Deuteriated derivative.

TABLE 2

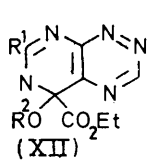
U.v. spectra [a]

Compound	Solvent	Species [b]	$\lambda_{max.}$/nm						log ε				
(XI; R = $N[CH_2]_5$)	Hexane	ANM	240		282		455	*480*	4·3	4·33		3·87	*3·85*
	H_2O, pH 6·0	HNM [c]			278		415		4·33		3·66		
(XI; R = NMe_2)	Hexane	ANM	238		278	*412*	435	460 *484*	4·62	4·59	*3·83*	3·98	3·96
											3·65		
	H_2O, pH 6·0	HNM [c]	277		415				4·03		3·56		
(XI; R = Cl)	Hexane	ANM	220	*318*	326	*339*			4·66	*4·37*	4·41		*4·34*
	H_2O, pH 6·0	HNM [c]	250		357				4·09	3·75			

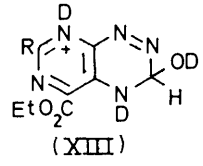
[a] Inflexions and shoulders in italics. [b] ANM = anhydrous neutral molecule, HNM = hydrated neutral molecule. [c] Obtained by dissolving anhydrous compound in the buffer solution and allowing equilibrium to be established.

Covalent Hydration.—Comparison of the u.v. spectra of the compounds (XI; R = Cl, NMe_2, or $N[CH_2]_5$), after equilibration in aqueous buffer pH 6·0, with those for analogous 5-trifluoromethylpyrimido[5,4-*e*]-*as*-triazines [5] indicated that hydration occurred in the pyrimidine ring at the 5,6-position (Table 2). This was confirmed by ^1H n.m.r. spectroscopy of the 7-chloro-derivative in $(CD_3)_2CO$–D_2O: the signal for the 3-proton, although showing an upfield shift within 10 min of addition of the D_2O, remained in the aromatic region (τ 0·57). The rate of addition of water varied as expected with the nature of the 7-substituent,[3] the chloro-compound taking only 0·2 h for complete hydration and the amino-derivatives taking up to 30 h. Isolation of the 7-chloro-hydrate (XII; R^1 = Cl, R^2 = H) was attempted by freeze-drying an aqueous solution, but the solid obtained decomposed rapidly.

N.m.r. studies of compounds (XI; R = Cl or NMe_2) in $(CD_3)_2CO$–20% DCl showed rapid formation of one species in each case, which gradually changed completely to a more stable entity. Signals for the 3-proton and the ester group were present in the spectra of the rapidly formed species and the final product (see Table 3), the former occurring at τ 1·1—1·3 in both cases. This eliminated the possibility of formation of the 3,4-deuteriated cation (XIII; R = Cl or NMe_2), the 3-proton of which would absorb at τ *ca.* 4·80. Recently



(XII)



(XIII)

it has been reported that 7-chloro-4-trifluoromethylpteridine (III; R = Cl) gives a 5,6,7,8-dihydrated cation which is rapidly converted into a 3,4-monohydrated cation.[4] We suggest that the presence of a triazine ring prevents analogous 1,2,3,4-hydration and addition of D_2O occurs first across the 7,8-bond to form the cation (XIV; R = Cl), which is rapidly converted into the more stable 5,6-deuteriated cation (XV; R = Cl). Rapid formation of the least stable hydrate followed by conversion into the most stable has been observed previously.[1,2,19]

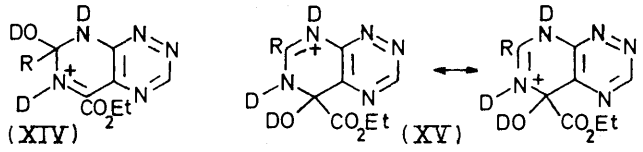
[17] E. Buncel and E. A. Symons, *Chem. Comm.*, 1970, 164.
[18] J. Clark, *Org. Mass Spectrometry*, 1972, **6**, 467.
[19] A. Albert, T. J. Batterham, and J. J. McCormack, *J. Chem. Soc.* (*B*), 1966, 1105.

TABLE 3
Hydration behaviour studies

Compound	Solvent	Chemical shifts (τ) [a,b] Ester CH_3	Ester CH_2	3-H	7- Subst.
(XI; R = Cl)	$(CD_3)_2CO$–20% DCl	8·73 [c]	5·68 [d]	1·27	
		8·63 [e]	5·58 [f]	1·15	
(XI; R = NMe_2)	$(CD_3)_2CO$–20% DCl	8·73 [c]	5·60 [d]	1·32	6·67
		8·60 [e]	5·47 [f]	1·18	6·57

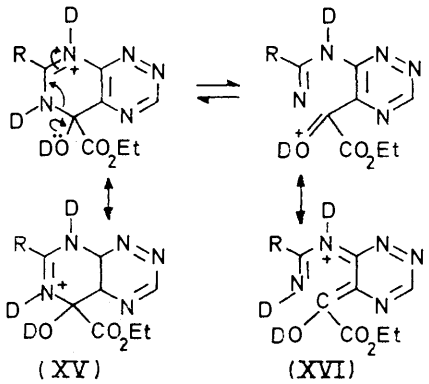
[a] Measured on a Varian EM-360 60 MHz spectrometer, at normal probe temperature, with tetramethylsilane as internal standard. [b] Signals are singlets unless stated otherwise. [c] Overlapping t, J 8 Hz, of the first-formed compound. [d] Overlapping q, J 8 Hz, of the first-formed compound. [e] t, J 8 Hz, of stable compound. [f] q, J 8 Hz, of stable compound.

Another possible explanation for the n.m.r. data is that the 5,6-deuteriated cation (XV; R = Cl) undergoes ring opening to give structure (XVI), which can be



(XIV) (XV)

stabilised as shown. However the stabilisation involves loss of an aromatic ring and the equilibrium should favour the cyclic structure. This conclusion is supported by the observed τ value for the 3-proton in a compound similar to (XVI), *viz.* 6-amino-*as*-triazine-5-carboxamide,[20] τ 0·85.



(XV) (XVI)

EXPERIMENTAL

Ethyl 5-Amino-2,6-dichloropyrimidine-4-carboxylate (VIII).—Ethyl 2,6-dichloro-5-nitropyrimidine-4-carboxylate (11·32 g), iron powder (11·32 g), and glacial acetic acid (100 ml) were stirred at 60° for 1 h. The solution was evaporated under reduced pressure, the residue taken up in water (100 ml), and the resulting suspension extracted with ether (4 × 100 ml). The extract was washed with dilute sodium hydroxide (100 ml), then with water (100 ml), dried ($MgSO_4$) and evaporated to give the *amine* (7·32 g), m.p. 114° [from petroleum (b.p. 80—100°)] (Found: C, 35·8; H, 3·2; N, 17·7. $C_7H_7Cl_2N_3O_2$ requires C, 35·6; H, 3·0; N, 17·9%).

Ethyl 5-Amino-2-chloro-6-hydrazinopyrimidine-4-carboxylate (IX).—A solution of the amino-ester (VIII) (2 g) in methanol (40 ml) was cooled to 4° and stirred during the dropwise addition of hydrazine hydrate (0·85 g) in methanol (5 ml). The mixture was stirred overnight and then filtered. Crystallisation of the precipitate from methanol yielded the *hydrazino-compound* (1·2 g), m.p. 274—276° (decomp.) (Found: C, 36·0; H, 4·3; N, 30·2. $C_7H_{10}ClN_5O_2$ requires C, 36·2; H, 4·4; N, 30·4%).

Ethyl 5-Amino-2-chloro-6-isopropylidenehydrazinopyrimidine-4-carboxylate.—The hydrazino-ester (IX) (0·10 g) was heated under reflux with acetone (20 ml) for 0·25 h. Evaporation followed by crystallisation of the residue from benzene gave the *isopropylidene derivative* (0·08 g), m.p. 197—198° (Found: C, 45·0; H, 5·4; N, 26·1. $C_{10}H_{14}ClN_5O_2$ requires C, 44·1; H, 5·2; N, 25·9%).

Ethyl 7-Chloro-1,2-dihydropyrimido[5,4-e]-as-*triazine-5-carboxylate* (X).—The hydrazino-ester (IX) (1 g), triethyl orthoformate (16 ml), and concentrated hydrochloric acid (*d* 1·18; 0·8 ml) were stirred for 1 h at 24°. The resulting suspension was filtered and the precipitate (hydrochloride) was dried at 70°, then ground to a fine powder, and treated with aqueous 20% sodium hydrogen carbonate (10 ml) to give the *dihydro-compound* (0·47 g), m.p. 278° (from acetone) (Found: C, 40·1; H, 3·3; N, 28·3. $C_8H_8ClN_5O_2$ requires C, 39·7; H, 3·3; N, 29·0%).

Ethyl 7-Chloropyrimido[5,4-e]-as-*triazine-5-carboxylate* (XI; R = Cl).—A suspension of the dihydro-compound (X) (0·1 g) in methylene chloride (10 ml) was stirred during the addition of 1-chlorobenzotriazole (0·063 g) in methylene chloride (5 ml). The mixture was immediately evaporated under reduced pressure at 24°. The residue was extracted with boiling light petroleum (b.p. 60—80°) to yield the *pyrimidotriazine* (0·018 g), m.p. 87° (Found: C, 40·3; H, 2·7; N, 29·3. $C_8H_6ClN_5O_2$ requires C, 40·0; H, 2·5; N, 29·3%).

Ethyl 7-Dimethylaminopyrimido[5,4-e]-as-*triazine-5-carboxylate* (XI; R = NMe_2).—(*a*) The chloropyrimidotriazine (XI; R = Cl) (0·01 g) in t-butyl alcohol (10 ml) was stirred during the addition of anhydrous dimethylamine (0·01 g) and for a further 5 min. The solution was evaporated under reduced pressure and the residue extracted with boiling petroleum (50 ml; b.p. 60—80°). Concentration of the extract gave the *dimethylamino-compound* (0·008 g), m.p. 124° (Found: C, 48·4; H, 5·1%; M^+, 248. $C_{10}H_{12}N_6O_2$ requires C, 48·3; H, 4·9%; M, 248).

(*b*) The chlorodihydropyrimidotriazine (X) (0·1 g) and dimethylformamide (25 ml) were heated at 140° for 24 h. The solution was evaporated under reduced pressure and the residue treated with chloroform (5 ml). Insoluble material was filtered off and the filtrate was applied in bands to glass plates coated with a 1 mm layer of silica. Development with chloroform gave a red front-running band, which was scraped off and extracted with chloroform. Evaporation of the extract and extraction with petroleum (b.p. 60—80°) yielded the dimethylaminopyrimidotriazine (0·015 g), m.p. 124°.

Ethyl 7-Piperidinopyrimido[5,4-e]-as-*triazine-5-carboxylate* (XI; R = $N[CH_2]_5$).—The chloropyrimidotriazine (XI; R = Cl) (0·023 g) in anhydrous benzene (10 ml) was stirred during the addition of redistilled piperidine (0·016 g), and for a further 5 min. The solution was evaporated and the

[20] C. Temple, jun., C. L. Kussner, and J. A. Montgomery, *J. Org. Chem.*, 1969, **34**, 2102.

residue extracted with boiling petroleum (3 × 25 ml; b.p. 60—80°). Concentration of the extract followed by refridgeration gave the *piperidino-compound* (0·017 g), m.p. 102° (Found: C, 53·9; H, 5·7%; M^+, 288. $C_{13}H_{16}N_6O_2$ requires C, 54·05; H, 5·6%; M, 288).

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