Triazines and Related Products, Part 22.[1] Synthesis and Reactions of Imidazo[5,1-*c*][1,2,4]triazines

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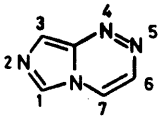
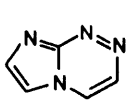
5-Diazoimidazole-4-carboxamide couples with reactive methylenic substrates to afford a series of imidazolylhydrazones which cyclise in acid or alkali to imidazo[5,1-*c*][1,2,4]triazines. Hydrazones with cyano-substituents cyclise in acid to yield 7-aminoimidazotriazines whereas hydrazones with acetyl groups undergo acidic dehydration to form bicycles with a 7-methylene substituent. In basic conditions, hydrazones with a reactive ester group cyclise to imidazotriazin-7(4*H*)-ones with loss of an alcohol moiety. Ethyl 7-amino-3-carbamoylimidazo[5,1-*c*][1,2,4]-triazine-6-carboxylate hydrolyses in boiling 2N-hydrochloric acid, forms an *N*-acetyl derivative, and reacts with secondary heteroalicyclic amines to form amides.

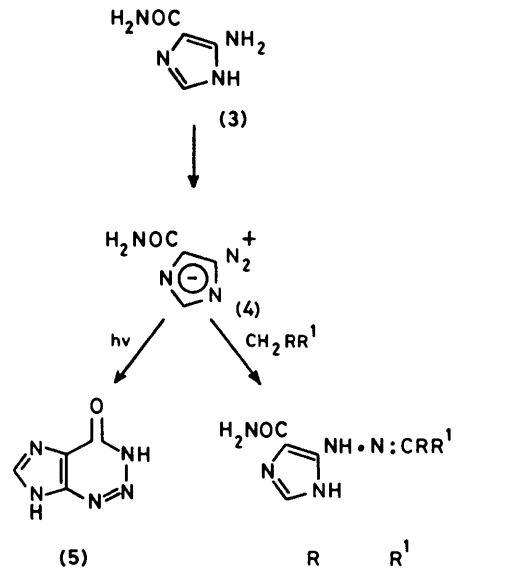
PREVIOUS papers in this series have described the chemistry of 1,2,4-triazines fused to a tetrazole [2] or 1,2,4-triazole [2-4] ring. Of the two possible bicyclic systems with a bridgehead nitrogen formed by fusion of an imidazole ring to the *c* bond of a 1,2,4-triazine [(1) and (2)] the least well-reported is the imidazo[5,1-*c*][1,2,4]triazine arrangement (1) examples of which have only recently been described.[5-8] We have concentrated on the synthesis of imidazotriazines (1) with a carboxamide


(1) [5,1-*c*]


(2) [2,1-*c*]

function at C-3 since these derivatives, and their acyclic precursors, can be envisaged as structural modifications of 5-aminoimidazole-4-carboxamide (3); they are thus potential inhibitors of *de novo* purine biosynthesis.[9] Such considerations perhaps motivated other workers [7,8] who prepared a limited number of fused imidazole carboxamides of this type: these efforts will be discussed in the light of the present findings.

Although 5-diazoimidazole-4-carboxamide (4) can be prepared by diazotisation of the amine (3) in an excess of nitrous acid, it is a troublesome synthon since it cyclises slowly in the dark, but more rapidly in the light, to 2-azahypoxanthine (5).[10,11] (However, see the following paper for a re-examination of this reaction.) Despite the competing intra-molecular reaction the diazoimidazole couples preferentially with methylenic substrates in ethanol in the dark to afford a series of hydrazones (6)—(15) in generally satisfactory yields (70—95%) (Scheme 1). The reactions with benzoylacetone and diethyl malonate proceed sluggishly and the hydrazones (13) and (15) are isolated in poor yields. The hydrazones are acidic and their long-wavelength electronic absorption maxima in the range 340—410 nm undergo a bathochromic shift on addition of sodium hydroxide or ferrous sulphate (see Table 1). The hydrazone (6) formed from ethyl cyanoacetate formed a pyridinium salt in pyridine and a potassium salt in ethanolic potassium hydroxide. Rapid re-acidification of the potassium salt with N-hydrochloric acid liberated an unstable modified hydrazone with spectroscopic properties different from those of the original material particularly in the N–H and C=O regions of the i.r. spectrum. Similar behaviour in other azolohydrazones has been attributed to the co-existence of different geometrical isomers.[4] When potassium hydroxide solutions of the hydrazones



	R	R^1
(6)	CO_2Et	CN
(7)	CN	CN
(8)	$CONH_2$	CN
(9)	CO_2Et	Bz
(10)	CO_2Me	Ac
(11)	CO_2Et	Ac
(12)	Ac	Ac
(13)	Bz	Ac
(14)	CO_2Et	$COCH_2CO_2Et$
(15)	CO_2Et	CO_2Et

SCHEME 1

formed from reactive methylenic esters were examined by u.v. spectroscopy, progressive changes occurred consequent upon cyclisation (see later). Because of the instability of the hydrazones it was not, in general, possible to crystallise them to analytical purity: instead they were characterised by their mass spectra which in all cases confirmed the presence of the appropriate molecular ions, and other spectral characteristics (Tables 1 and 2).

Several of these hydrazones have been described by Kočevar and co-workers,[8] but contrary to their experience we find that most of the hydrazones cyclised to imidazo[5,1-*c*][1,2,4]triazines in acid conditions. For example, hydrazone (6) although stable in hot ethanol alone cyclised in boiling 50% ethanolic acetic acid to yield an acetic acid solvate of the aminoester (16). That cyclisation had involved the cyano rather than the ester function was evidenced by the spectroscopic properties of

TABLE 1

Electronic absorption and i.r. spectra of imidazolylhydrazones, pyrazolylhydrazones, imidazo[5,1-*c*][1,2,4]triazines, and pyrazolo[4,3-*c*]pyridazines

Compound	Electronic absorption spectra [a] Solvent	$\lambda_{max.}$/nm					Medium	I.r. spectra [b] $\nu_{max.}$(cm^{-1})
(6)	A	240	395				E	3 350 (NH), 2 250 (C≡N), 1 710 (CO_2Et), 1 650 ($CONH_2$)
	B	240 *	393					
	C	241	404					
	D	240	404					
K salt	A	240	403				E	3 370, 3 150(NH), 2 200(C≡N), 1 625(C=O)
Pyridinium salt	A	247	250	256	263 *	403	E	3 480(NH), 3 100—2 400(NH), 2 200(C≡N), 1 670(CO_2Et), 1 645($CONH_2$)
Isomer (hydrate)							E	3 340, 3 100(NH), 3 000—2 500 (bonded NH/OH), 2 200(C≡N), 1 715(CO_2Et), 1 650($CONH_2$)
(7)	A [c]	395					E	3 380(NH), 3 100—2 800 (bonded NH), 2 260(C≡N), 1 640($CONH_2$)
	B	225 *	250 *	295 *	395			
	C	256	324	403				
(8)	A	236 *	290 *	405			E	3 380(NH), 3 000—2 700 (bonded NH), 2 200 (C≡N), 1 700, 1 650($CONH_2$)
(9)	A	255	345				E	3 450, 3 300(NH), 1 715(CO_2Et), 1 630($CONH_2$)
	C	426						
	D [d]	430						
(10)	A	245	341				E	3 500(NH), 3 300—3 150 (bonded NH), 1 715(CO_2Me, Ac), 1 630($CONH_2$)
	B	225	250 *	333				
	C	254	402					
(11)	A	246	342				E	3 470(NH), 3 280—3 150 (bonded NH), 1 705(CO_2Et, Ac), 1 630($CONH_2$)
	B	225	250 *	333				
	C	257	405					
(12)	A	244	345				E	3 400, 3 390, 3 190(NH), 1 680(Ac), 1 650($CONH_2$)
	B	225	255	335				
	C	256	405					
	D	261	290 *	424				
(13)	A	228 *	252	348			E	3 400(NH), 3 300—3 200 (bonded NH), 1 670(Bz, Ac), 1 640($CONH_2$)
(14)	A	230 *	250	343			E	3 450, 3 350(NH), 3 160 (bonded NH), 1 722, 1 695(CO_2Et, C=O), 1 640($CONH_2$)
(15)	A	227 *	242 *	262 *	362		E	3 450(NH), 3 100 (bonded NH), 1 700(CO_2Et), 1 665($CONH_2$)
(16)	A	244	307 *	316	330 *	381	E	3 390(NH), 3 170 (bonded NH), 1 695(CO_2Et), 1 630($CONH_2$)
	B	244	307 *	316	330 *	381		
(17)	A	242	305 *	312	325 *	390	E	3 440, 3 330, 3 260(NH), 3 130 (bonded NH), 2 250(C≡N), 1 660($CONH_2$)
	B	242	305 *	312	325 *	390		
(18)	A	246	313	325 *	390		E	3 400, 3 350, 3 250(NH), 3 150 (bonded NH), 1 680, 1 660($CONH_2$)
	B	246	313	325 *	390			
(19)	A	253	290 *	368			E	3 300—3 100 (bonded NH), 1 705(CO_2Et), 1 630($CONH_2$)
(25)	A	232	267	278 *	296 *	367	E	3 360(NH), 3 150 (bonded NH), 1 722 (CO_2Me), 1 665($CONH_2$)
$MeCO_2H$ solvate							E	3 370, 3 300(NH), 3 200 (bonded NH), 2 600—2 400 (bonded OH), 1 710(CO_2Me), 1 695(Ac), 1 642($CONH_2$)
Acetyl-derivative	A	268	295 *	372			E	3 350, 3 280(NH), 1 729, 1 715(CO_2Me), 1 695(Ac)
(26)	A	235	267	278	298	367	F	3 330(NH), 3 180 (bonded NH), 1 720(CO_2Et), 1 669($CONH_2$)
EtOH solvate	A	225	246	338			E	3 495, 3 390, 3 280(NH), 3 150 (bonded NH), 1 700(CO_2Et), 1 650($CONH_2$), 1 140(OEt)
(27)	A	242	253 *	270 *	279 *	366	E	3 460(NH), 3 220—3 120 (bonded NH), 1 670(Ac, $CONH_2$)
(28) Hydrate	A	226	258	364			E	3 460, 3 400(NH), 3 200 (bonded NH/OH), 1 650(Bz, $CONH_2$)

TABLE 1 (*continued*)

Compound	Solvent	Electronic absorption spectra [a] $\lambda_{max.}$/nm					Medium	I.r. spectra [b] $\nu_{max.}$(cm^{-1})
(29) Hydrate	A	241	297	385			E	3 340(NH), 3 150 (bonded NH/OH), 1 700(CO_2Et), 1 650($CONH_2$)
(32)	A	243	345				E	3 420, 3 350, 3 200(NH), 1 720(CO_2Me), 1 660(Ac, $CONH_2$)
(33)	A	244	345				E	3 500, 3 400, 3 250(NH), 1 730, 1 720(CO_2Et), 1 670(Ac, $CONH_2$)
(34)	A	238	281	290 *	404		E	3 460, 3 400, 3 340(NH), 3 150 (bonded NH), 2 207(C≡N), 1 720(CO_2Et), 1 640($CONH_2$)
(35)	A	246	312	350 *	400 *		E	3 500—3 200 (bonded NH), 1 710(CO_2Me), 1 640($CONH_2$)
(36)	A	246	313	350 *	400 *		E	3 450, 3 200(NH), 1 715(CO_2Et), 1 670($CONH_2$)
(37) [e]	A	228	285	290 *	361		E	3 460(NH), 3 330—3 100 (bonded NH/OH), 2 230(C≡N), 1 695(C=O), 1 675, 1 660($CONH_2$)
(38)	A	244	288 *	298	310 *	382	E	3 410(NH), 2 220(C≡N), 1 673(C=O, $CONH_2$)
	D	245	293	310 *	380			
(39)	A	240 *	257	296	378		E	3 400, 3 270(NH), 1 670(Bz, C=O), 1 635($CONH_2$)
	D	255	328	390				
(40) Hemihydrate	A	242	250 *	289	376		E	3 500, 3 450, 3 350(NH), 3 150(bonded NH), 1 710(Ac), 1 665(C=O, $CONH_2$)
	D	248	315	382				
(41) Hemihydrate	A	240	295	385			E	3 380(NH), 3 200 (bonded NH/OH), 1 700(CO_2Et) 1 670(C=O, $CONH_2$)
	D	267	320	398				
(42) Hydrate	A	239	279	373			E	3 500, 3 350(NH), 3 160 (bonded NH/OH), 1 725(CO_2Et), 1 660(C=O, $CONH_2$)
	D	250	301	382				
(43) Hydrate	A	239	250 *	279	375		E	3 450, 3 300(NH), 1 662(C=O, CO_2H, $CONH_2$)
	D	248	296	388				
(44)	A	240	250 *	286	379		E	3 400(NH), 3 220 (bonded NH), 1 695($CONH_2$), 1 660(C=O, $CONH_2$)
	D	242	300	310 *	381			
(46)							E	3 498, 3 370, 3 150(NH), 1 700(CO_2Et), 1 665(C=O, $CONH_2$)
(47)	A	240 *	314	328 *	386		E	3 400, 3 340(NH), 1 720(CO_2Et), 1 685(Ac), 1 635($CONH_2$)
(49)	A	250 *	309	382			E	3 365(NH), 3 250(bonded NH), 1 660(C=O), 1 635($CONH_2$)
	B	276	379					
(50) Hemihydrate	A	250 *	310	381			E	3 370, 3 290(NH), 3 150 (bonded NH), 1 675(C=O), 1 625($CONH_2$)
	B	278	378					
(51)	A	250 *	314	382			E	3 440(NH), 3 280, 3 100 (bonded NH), 1 665(C=O), 1 640($CONH_2$)
	B	278	381					
(52)	A	250	311	382			E	3 360, 3 290, 3 150(NH), 1 670(C=O), 1 635($CONH_2$)
	B	245 *	282	382				
(53)	A	244	302	400			E	3 400(NH), 3 150, 3 050 (bonded NH), 1 680($CONH_2$)
(54)	A	260	313	325 *	428		E	3 400—3 200 (bonded NH), 1 660($CONH_2$)

Solvents and media: A, 95% ethanol; B, 95% ethanol + 2N-hydrochloric acid; C, 95% ethanol + saturated $Fe^{II}SO_4$; D, 95% ethanol + 2N-sodium hydroxide; E, potassium bromide disc; F, chloroform solution

[a] Spectra recorded on a Unicam SP 8000. [b] Spectra recorded on a Unicam SP 200. [c] Also shows peaks of cyclic product (17). [d] Also shows peaks of cyclic product (39). [e] Contains 1.5 molecules of water of crystallisation.

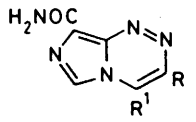
* Inflexion.

the solvate (Tables): the unsolvated amine was obtained by stirring the solvate in water, ethanol, or dimethylformamide. Hydrazones (7) and (8) from malononitrile and cyanoacetamide also smoothly cyclised to aminoimidazotriazines (17) and (18) respectively in boiling ethanolic acetic acid. Hydrazone (7) also cyclised on attempted crystallisation from hot ethanol, or even in cold ethanol ($t_{\frac{1}{2}}$ *ca.* 1 h at 25 °C); in the latter case the rate could be greatly accelerated by exposure of the solution to sunlight. In contrast, the hydrazone (9) formed from ethyl benzoylacetate cyclised only partially on prolonged boiling in ethanolic acetic acid and a pure sample of the phenylimidazotriazine (19) could not be obtained.

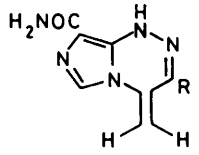
The acetylhydrazones (10) and (11) also changed in ethanolic acetic acid. In both cases loss of a molecule of water was confirmed by elemental and mass spectroscopic analysis of the products. However, contrary to expectations the products were not the 7-methylimidazotriazines (20) and (21) respectively since their ^{1}H n.m.r. spectra (Table 2) showed no absorptions for the 7-methyl groups. These compounds are, in fact, the 7-methylene tautomers (25) and (26) since their spectra showed an AB pattern integrating for two protons in both trifluoroacetic acid and $(CD_3)_2SO$. A compound formed by cyclisation of the hydrazone (12) and formulated as the 7-methylimidazotriazine (22) has been reported recently:[7] apparently the correct methylene structure (27) for this product was not suspected since the n.m.r. spectrum was not recorded. The spectrum in trifluoroacetic acid clearly indicated its relationship to the methylenic esters (25) and (26).

Unfortunately, derivatives (25)—(27) were insoluble in pyridine so the influence of base on the equilibrium

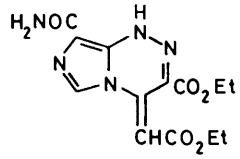
between methyl and methylene tautomers could not be assessed. Similarly, the products formed by acid cyclisation of hydrazones (13) and (14) are probably not the expected imidazotriazines (23) and (24) respectively but rather their 7-methylene (28) and 7-methine (29) tautomers respectively, although these two compounds



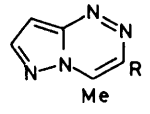
	R	R^1
(16)	CO_2Et	NH_2
(17)	CN	NH_2
(18)	$CONH_2$	NH_2
(19)	CO_2Et	Ph
(20)	CO_2Me	Me
(21)	CO_2Et	Me
(22)	Ac	Me
(23)	Bz	Me
(24)	CO_2Et	CH_2CO_2Et



(25) R = CO_2Me
(26) R = CO_2Et
(27) R = Ac
(28) R = Bz



(29)

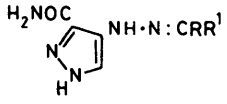


(30) R = CO_2Et
(31) R = Ac

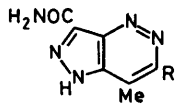
were again too insoluble for n.m.r. examination. Certainly, acid cyclisation of the hydrazone formed from diazoimidazolecarboxamide and benzoylacetone (13) involves participation of the acetyl rather than the benzoyl group in the dehydrative step, and the stability of the methylene tautomer (28) could provide the driving force for this electronically unfavoured cyclisation. The presence of a 6-benzoyl function in (28) was confirmed by an abundant phenylacylium ion peak (*m/e* 105) in its mass spectrum.

The opposing factors which influence tautomer populations in 1,2,4-triazines (in particular amino- or imino-triazinones) have been discussed by Le Count and Taylor.[12] In-plane lone-pair interactions of the neighbouring sp^2 hybridised nitrogen atoms (N-4 and N-5) of the triazine ring which destabilise a formal N : N double bond would favour the methylene state: in contrast conjugation in the triazine ring imparting heteroaromatic stability on the bicyclic system would favour the 7-methyl arrangement. An additional feature unique to the present examples—intramolecular hydrogen bonding involving the carboxamide group—could possibly be important. The oxygen atom of the 3-carbamoyl substituent in derivatives (25)—(29) could form a hydrogen bond with the N(4)–H and stabilise the methylene forms. Apparent support for this proposition was afforded by an examination of the ^1H n.m.r. spectra (in $CDCl_3$) of two related 7-methylpyrazolo[5,1-*c*][1,2,4]-triazines (30) and (31) [13] which, lacking a carboxamide group at C-3, show no evidence for methylene tautomers (Table 2).

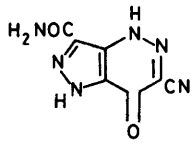
To obtain further insight into the role (if any) of the carboxamide-group in this type of tautomerism 4-diazopyrazole-3-carboxamide [14] was coupled with methyl and ethyl acetoacetate to yield unstable hydrazones (32) and (33) which smoothly cyclised in refluxing ethanol with C–C bond formation to afford the pyrazolo[4,3-*c*]-pyridazines (35) and (36) respectively. These esters



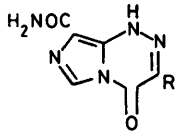
	R	R^1
(32)	CO_2Me	Ac
(33)	CO_2Et	Ac
(34)	CO_2Et	CN



(35) R = CO_2Me
(36) R = CO_2Et



(37)



(38) R = CN
(39) R = Bz
(40) R = Ac
(41) R = $COCH_2CO_2Et$
(42) R = CO_2Et
(43) R = CO_2H
(44) R = $CONH_2$

exist exclusively in their 7-methyl forms as adjudged by their ^1H n.m.r. spectra in $(CD_3)_2SO$ despite the apparently favourable juxtaposition of carboxamide and ring nitrogen for hydrogen bonding. We conclude that intramolecular hydrogen bonding involving the carbamoyl group is only one of the factors which determine tautomer populations in these bicyclic systems and that this effect, together with the loss of heteroaromatic stability imparted by additional bridgehead aza-substitution,[15]

TABLE 2

^{1}H N.m.r. spectra [a] of imidazolylhydrazones, imidazo[5,1-*c*][1,2,4]triazines, pyrazolo[5,1-*c*][1,2,4]triazines, and pyrazolo-[4,3-*c*]pyridazines

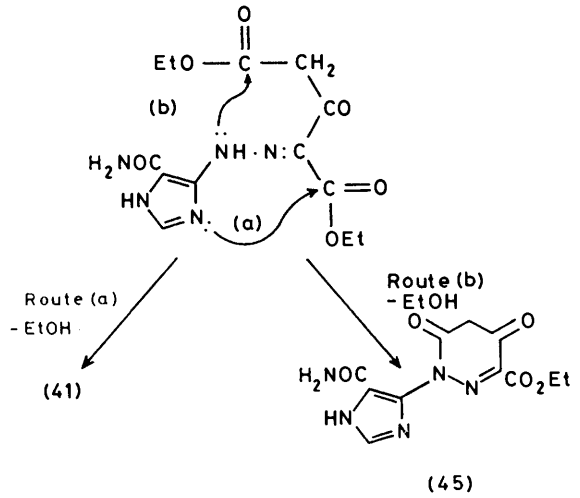
Compound	Solvent	δ Values
(6) [b]	A	8.83 (1 H, s, H-2), 8.1br (NH), 4.62 (2 H, q, *J ca.* 8 Hz, CH_2), 1.50 (3 H, t, *J ca.* 8 Hz, CH_3),
(10)	B	7.9 (1 H, s, H-2), 7.1br (NH), 3.78 (3 H, s, OCH_3), 2.14 (3 H, s, $COCH_3$)
(11) [b]	B	7.81 (1 H, s, H-2), 7.1br (NH), 4.22 (2 H, q, *J ca.* 8 Hz, CH_2), 2.08 (3 H, s, $COCH_3$), 1.27 (3 H, t, *J ca.* 8 Hz, CH_2·CH_3)
(16)	A	9.22 (1 H, s, H-1), 4.70 (2 H, q, *J ca.* 8 Hz, CH_2), 1.56 (3 H, t, *J ca.* 8 Hz, CH_3)
$MeCO_2H$ solvate	A	9.20 (1 H, s, H-1), 4.66 (2 H, q, *J ca.* 8 Hz, CH_2), 2.22 (3 H, s, CH_3CO_2H), 1.52 (3 H, t, *J ca* 8 Hz, CH_2·CH_3)
(25)	A	9.13 (1 H, s, H-1), 6.50 (1 H, d, *J ca.* 6 Hz, CH), 5.96 (1 H, d, *J ca.* 6 Hz, CH), 4.13 (3 H, s, CH_3)
$MeCO_2H$ solvate	A	9.13 (1 H, s, H-1), 6.48 (1 H, d, *J ca.* 6 Hz, CH), 5.94 (1 H, d, *J ca.* 6 Hz, CH), 4.10 (3 H, s, CH_3), 2.27 (3 H, s, CH_3CO_2H)
(26)	A	9.10 (1 H, s, H-1), 6.55 (1 H, d, *J ca.* 6 Hz, CH), 6.0 (1 H, d, *J ca.* 6 Hz, CH), 4.61 (2 H, q, *J ca*, 8 Hz, CH_2), 1.51 (3 H, t, *J ca.* 8 Hz, CH_3)
(27)	A	9.11 (1 H, s, H-1), 7.9br (NH), 6.67 (1 H, d, *J ca.* 6 Hz, CH), 5.92 (1 H, d, *J ca.* 6 Hz, CH), 2.74 (3 H, s, CH_3)
(30) [c]	C	8.47 (1 H, d, *J ca.* 3 Hz, H-2), 7.37 (1 H, d, *J ca.* 3 Hz, H-3), 6.60 (2 H, q, *J ca.* 8 Hz, CH_2), 3.23 (3 H, s, CH_3), 1.50 (3 H, t, *J ca.* 8 Hz, CH_2·CH_3)
(31) [c]	C	8.45 (1 H, d, *J ca.* 3 Hz, H-2), 7.32 (1 H, d, *J ca.* 3 Hz, H-3), 3.24 (3 H, s, CH_3), 2.99 (3 H, s, $COCH_3$)
(32)	B	8.13 (1 H, s, H-5), 6.83br (NH), 3.27 (3 H, s, OCH_3), 2.14 (3 H, s, $COCH_3$)
(33)	B	8.21 (1 H, s, H-5), 4.16 (2 H, q, *J ca.* 8 Hz, CH_2), 2.04 (3 H, s, $COCH_3$), 1.29 (3 H, t, *J ca.* 8 Hz, CH_2·CH_3)
(35)	B	6.9br (NH), 3.40 (3 H, s, OMe), 2.0[illegible] (3 H, s, CH_3)
(36)	B	4.30 (2 H, q, *J ca.* 8 Hz, CH_2), 2.19 (3 H, s, CH_3), 1.44 (3 H, t, *J ca.* 8 Hz, CH_2·CH_3)
(38)	A	8.80 (1 H, s, H-1)
(40) Hemihydrate	A	8.98 (1 H, s, H-1)
(41) Hemihydrate	A	8.97 (1 H, s, H-1), 4.45 (2 H, q, *J ca.* 8 Hz, CH_2·CH_3), 4.35 (2 H, s, CH_2), 1.40 (3 H, t, *J ca.* 8 Hz, CH_2·CH_3)
(42) Hydrate	B	8.51 (1 H, s, H-1), 7.5br (NH), 4.35 (2 H, q, *J ca.* 8 Hz, CH_2), 1.35 (3 H, t, *J ca.* 8 Hz, CH_3)
(47)	A	9.17 (1 H, s, H-1), 4.65 (2 H, q, *J ca.* 8 Hz, CH_2), 2.60 (3 H, s, $COCH_3$), 1.50 (3 H, t, *J ca.* 8 Hz, CH_2·CH_3)
(49)	A	8.78 (1 H, s, H-1), 7.70br (NH), 3.80br (4 H, m, CH_2), 1.95br (6 H, m, CH_2)
(50) Hemihydrate	A	8.90 (1 H, s, H-1), 4.0br (4 H, m, CH_2), 2.30br (4 H, m, CH_2)
(51)	A	8.70 (1 H, s, H-1), 8.2br (NH), 4.4—3.8br (8 H, m, CH_2)

Solvents: A, Trifluoroacetic acid; B, [$^2H_6$]dimethyl sulphoxide; C, deuteriochloroform.
[a] Recorded on a Varian A–60A spectrometer. [b] Ref. 8. [c] Ref. 13.

tips the balance in favour of the methylene forms in the imidazotriazine-3-carboxamide series.

The hydrazone (34) prepared from 4-diazopyrazole-3-carboxamide and ethyl cyanoacetate cyclised in refluxing 70% aqueous ethanol with involvement of the ester rather than the cyano-group. The i.r. spectrum of the product, the pyrazolopyridazine-7(4*H*)-one (37), showed $\nu_{C\equiv N}$ at 2 230 cm^{-1} and $\nu_{C=O}$ at 1 695, 1 675, and 1 660 cm^{-1}. Similarly, when the imidazolylhydrazone (6) was boiled in 50% ethanolic pyridine or stirred with cold 1% alcoholic potassium hydroxide the imidazotriazinone (38) was formed. The cyclic product (39) has previously been reported to be formed from the hydrazone (9) and acid.[8] When this cyclisation was repeated it was found that at the end of the acid treatment the product was mainly unchanged hydrazone; cyclisation of the bulk of the hydrazone only occurred when the reaction mixture was basified with potassium hydroxide. Both the hydrazones (10) and (11) also cyclised under the influence of organic or inorganic bases to yield the same 6-acetylimidazotriazinone (40).

In aqueous alkali, hydrazone (14) cyclised with loss of ethanol to yield a product tentatively assigned structure (41) (Scheme 2; route a) on the grounds that its u.v. spectrum is nearly identical to that of the related triazinones (38)—(40): however the isomeric pyridazine-dione structure (45) (Scheme 2; route b) cannot be excluded on the spectroscopic evidence. Although hydrazone (15) was essentially unchanged in acid it readily cyclised in base to the oxo-ester (42). This

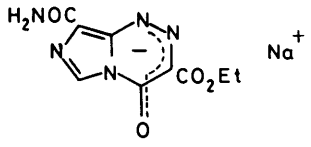


SCHEME 2

oxo-ester was sufficiently strongly acidic to dissolve in aqueous sodium hydrogen carbonate from which a sodium salt (46) deposited. Other triazin-7(4*H*)-ones prepared in the course of this work were also acidic and

their u.v. spectra underwent pronounced bathochromic shifts on addition of alkali (see Table 1). Hydrolysis of the oxo-ester in cold aqueous sodium hydroxide afforded a solution of the sodium salt of the oxo-acid (43) from which the free acid was liberated on acidification. The mass spectrum of the acid did not show a molecular ion corresponding to the expected constitution $C_7H_5N_5O_4$ (*m/e* 223): instead the highest mass ion corresponded to formula $C_6H_5N_5O_2$ ($M^+ - CO_2$). Decarboxylation of the acid was also observed above its m.p

Partial hydrolysis of the cyano-group of the oxo-cyanotriazine (38) was achieved in refluxing polyphosphoric acid: the product was the oxo-amide (44).

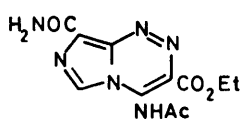


(46)

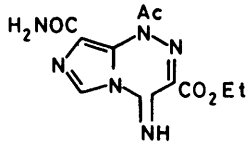
The hydrazone (8) did not afford the expected triazinone (38) in boiling pyridine or morpholine presumably because the carboxamide function is less susceptible to nucleophilic attack by the imidazole ring nitrogen (compared to ester groups). With this exception cyclisation of all the imidazolylhydrazones conforms to the behaviour first recognised in related 1,2,4-triazolylhydrazones [4]—that is, in acid they yield the more *basic* derivatives whereas in base they form the more *acidic* products.

The imidazotriazin-7(4*H*)-ones (38)—(44) like the other bicycles described here decomposed with indistinct melting points and were frequently strongly associated with water as evidenced by the microanalytical data. Possibly these solvates were of the covalent variety. A by-product isolated in the synthesis of the methylene-triazine (26) was apparently a covalent ethanolate since its mass spectrum showed a molecular ion corresponding to (26) plus the elements of ethanol.

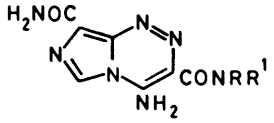
Both the 7-amino * and 6-ethoxycarbonyl groups of the amino-ester (16) can be efficiently transformed into other functionalities. Hydrolysis of the amino-group was effected in boiling 2N-hydrochloric acid; the product, the oxo-ester (42) was identical to that formed by alkaline cyclisation of hydrazone (15). The amino-ester (16) furnished a mono-acetyl derivative with a u.v. spectrum very similar to that of the starting amine. This compound is tentatively formulated as the 7-acetylamino-imidazotriazine (47) although the 4-acetyl-7(4*H*)-imino-structure (48) is a plausible alternative. Although the ester group of (16) did not react with saturated alcoholic ammonia at room temperature, a series of substituted amides (49)—(52) were efficiently prepared from the amino-ester and the appropriate secondary heteroalicyclic amines in refluxing benzene.



(47)



(48)

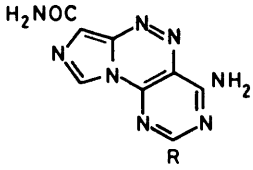


(49) R —(CH$_2$)$_5$— R^1

(50) —(CH$_2$)$_4$—

(51) —(CH$_2$)$_2$ O(CH$_2$)$_2$—

(52) —(CH$_2$)$_2$ NMe. (CH$_2$)$_2$—



(53) R = H

(54) R = NH$_2$

The 7-amino- and 6-cyano-substituents of the amino-nitrile (17) could be elaborated into a pyrimidine ring by reaction with formamide or guanidine at elevated temperatures. The amino- and diamino-pyrimidoimidazotriazines (53) and (54), respectively, thus formed were most efficiently purified by vacuum sublimation.

Ring-opening of the triazine ring of imidazo[5,1-*c*]-[1,2,4]triazines by hydrazine(s) will be described in a future paper in this series.

EXPERIMENTAL

Synthesis of Hydrazones.—5-Diazoimidazole-4-carboxamide (1.37 g) in absolute ethanol (25 ml) was stirred with ethyl cyanoacetate (1.7 g, 1.5 mol equiv.) in the dark for 5 days. The precipitated solid ethyl 2-(4-carbamoylimidazol-5-ylhydrazono)cyanoacetate (6) was collected (2.3 g) and had m.p. 230 °C (lit.,[8] m.p. 230 °C). The cyanoacetate afforded a *pyridine salt* from boiling pyridine, m.p. >320 °C (decomp.) (Found: C, 51.7; H, 4.5; N, 29.2. $C_9H_{10}N_6O_3 \cdot C_6H_5N$ requires C, 51.1; H, 4.6; N, 29.8%).

A suspension of hydrazone (6) (0.2 g) in ethanol (5 ml) formed a deep yellow solution when 1% ethanolic potassium hydroxide (3 ml) was added. The precipitated *potassium salt* of (6) was recovered in 60% yield. Careful neutralis-

* The 7-amino-tautomeric forms of the imidazotriazines (16)—(18) and (49)—(52) have been uncritically adopted since it is generally accepted that amino-groups in π-deficient heterocycles exist as such. However, the u.v.–visible spectra (Table 1) of the 7-aminoimidazotriazines are strikingly similar to those of the imidazotriazin-7(4*H*)-ones (38)—(44) and a substantial 7(4*H*)-imino-contribution cannot be discounted.[12]

ation of the salt with 1N-hydrochloric acid liberated a different hydrazone (see Table 1 for spectral properties) (Found: C, 40.2; H, 4.2. $C_9H_{10}N_6O_3 \cdot H_2O$ requires C, 40.3; H, 4.4%).

Also prepared from 5-diazoimidazole-4-carboxamide, a reactive methylenic compound (1.5 mol equiv.) in ethanol in the dark for 5—15 days were the following hydrazones: 2-(*4-carbamoylimidazol-5-ylhydrazono*)*malononitrile* (7) (85%), m.p. 240—245 °C (decomp.) for the unstable material washed with an excess of ethanol (Found: M^+ 203. $C_7H_5N_7O$ requires M, 203); 2-(*4-carbamoylimidazol-5-ylhydrazono*)*cyanoacetamide* (8) (90%), m.p. 190—195 °C (decomp.) from ethanol–dimethylformamide (Found: C, 38.1; H, 3.3; N, 42.8%; M^+, 221.066 11. $C_7H_7N_7O_2$ requires C, 38.0; H, 3.2; N, 44.3%; M, 221.066 07); ethyl 2-(4-carbamoylimidazol-5-ylhydrazono)benzoylacetate (9) (88%), m.p. 145—146 °C (from ethanol) (lit.,[8] m.p. 145 °C); *methyl* 2-(*4-carbamoylimidazol-5-ylhdrazono*)*acetoacetate* (10) (95%), m.p. 230—235 °C (decomp.) after washing with ethanol (Found: C, 42.3; H, 4.4%; M^+, 253.081 097. $C_9H_{11}N_5O_4$ requires C, 42.6; H, 4.3%; M, 253.080 93); ethyl 2-(4-carbamoylimidazol-5-ylhydrazono)acetoacetate, (11) (90%), m.p. 235—240 °C (decomp.) (lit.,[8] m.p. 205 °C); 3-(*4-carbamoylimidazol-5-ylhydrazono*)*pentane-2,4-dione* (12) (80%), m.p. 193—196 °C (decomp.) (lit.,[8] m.p. 196 °C); 3-(*4-carbamoylimidazol-5-ylhydrazono*)*benzoylacetone* (13) (90%), m.p. 156—160 °C (decomp.) after washing with ethanol (Found: M^+, 299. $C_{14}H_{13}N_5O_3$ requires M, 299); 1,1-bisethoxycarbonyl-2-(4-carbamoylimidazol-5-ylhydrazono)acetone (14) (90%), m.p. 182—184 °C (lit.,[8] m.p. 180—182 °C); *diethyl* 2-(*4-carbamoylimidazol-5-ylhydrazono*)*malonate* (15) (20%), m.p. 180—190 °C (decomp.) after washing with ethanol (Found: M^+, 297.107 31. $C_{11}H_{15}N_5O_5$ requires M, 297.106 44).

Methyl 2-(*3-Carbamoylpyrazol-4-ylhydrazono*)*acetoacetate* (32).—A suspension of 4-aminopyrazole-3-carboxamide (1.26 g) in 1N-hydrochloric acid (10 ml) was cooled to 0—5 °C and treated with sodium nitrite (1 mol equiv.) in water (3 ml). A tan precipitate of 4-diazopyrazole-3-carboxamide[14] slowly precipitated. The mixture was neutralised with an excess of sodium acetate trihydrate and stirred at 0—5 °C with methyl acetoacetate (1.16 g) for 2 h. The precipitated crude *hydrazonoacetoacetate* (1.85 g) had m.p. 235—240 °C (decomp.) and cyclised upon attempted crystallisation from ethanol (Found: M^+, 253. $C_9H_{11}N_5O_4$ requires M, 253). Similarly prepared were the following: *ethyl* 2-(*3-carbamoylpyrazol-4-ylhydrazono*)*acetoacetate* (33), from 4-diazopyrazole-3-carboxamide and ethyl acetoacetate, in 95% yield, m.p. (crude) 235 °C (decomp.) (Found: M^+, 267. $C_{10}H_{13}N_5O_4$ requires M, 267); *ethyl* 2-(*3-carbamoylpyrazol-4-ylhydrazono*)*cyanoacetate* (34), from 4-diazopyrazole-3-carboxamide and ethyl cyanoacetate, in 78% yield. The *hydrazone* crystallised from ethanol as yellow microcrystals, m.p. 240—245 °C (decomp.) (Found: C, 41.2; H, 4.0%; M^+, 250. $C_9H_{10}N_6O_3 \cdot 0.5H_2O$ requires C, 41.6; H, 4.2%; M, 250).

Acid-catalysed Cyclisations of Hydrazones.—*Ethyl* 7-*amino*-3-*carbamoylimidazo*[5,1-c][1,2,4]*triazine*-6-*carboxylate* (16). A solution of the hydrazone (6) (1.0 g) in ethanol (10 ml) and acetic acid (10 ml) was boiled for 0.5 h. Crystals of the *aminoimidazotriazine acetic acid solvate* (0.85 g) deposited and had m.p. 360 °C (decomp.) from acetic acid (Found: C, 42.4; H, 4.7; N, 26.8%; M^+, 250. $C_9H_{10}N_6O_3 \cdot CH_3CO_2H$ requires C, 42.6; H, 4.5; N, 27.0%; M, 310—60 [CH_3CO_2H]). Recrystallisation of the acetic acid solvate from dimethylformamide–ethanol mixture afforded the unsolvated *aminoimidazotriazine*, m.p. 350 °C (decomp.) (Found: C, 40.7; H, 4.5; N, 31.4%; M^+, 250. $C_9H_{10}N_6O_3$ requires C, 40.3; H, 4.5; N, 31.3%; M, 250).

The *acetyl-derivative* (47) was formed in 80% yield when the aminoimidazotriazine was boiled in acetic anhydride acetic acid (1 : 1) for 2 h. The light yellow product had m.p. 350 °C (decomp.) (Found: C, 44.8; H, 4.0; N, 28.9%; M^+, 292. $C_{11}H_{12}N_6O_4$ requires C, 45.2; H, 4.1; N, 28.8%; M, 292).

7-*Amino*-3-*carbamoyl*-6-*cyanoimidazo*[5,1-c][1,2,4]*triazine* (17). Cyclisation of the hydrazone (7) in a mixture of boiling ethanol and acetic acid (10 : 1) for 0.5 h afforded the deep yellow *aminonitrile* (95%), m.p. 350—360 °C (decomp.), from dimethylformamide–ethanol (Found: C, 41.2; H, 2.5; N, 48.0%; M^+, 203.055 55. $C_7H_5N_7O$ requires C, 41.4; H, 2.5; N, 48.3%; M, 203.055 01).

7-*Amino*-3-*carbamoylimidazo*[5,1-c][1,2,4]*triazine*-6-*carboxamide* (18). The hydrazone (8) (1.0 g) was boiled in acetic acid (15 ml) for 2 h. The precipitated yellow solid was collected, stirred with aqueous 1N-sodium hydroxide and washed with water. The *triazine-carboxamide* (85%) which could not be crystallised had m.p. 320 °C (decomp.) (Found: C, 38.0; H, 3.0%; M^+, 221. $C_7H_7N_7O_2$ requires C, 38.0; H, 3.2%; M, 221).

Ethyl 3-*carbamoyl*-7-*phenylimidazo*[5,1-c][1,2,4]*triazine*-6-*carboxylate* (19). The hydrazone (9) (1.0 g) was boiled in ethanolic acetic acid (1 : 1, 20 ml) for 24 h. The crude precipitated product, possibly the *triazine-carboxylate*, had m.p. 295 °C (decomp.) (*cf.* m.p. 145 °C for starting material) and could not be further purified (Found: M^+, 311. $C_{15}H_{13}N_5O_3$ requires M, 311).

Methyl 3-*carbamoyl*-4,7-*dihydro*-7-*methyleneimidazo*[5,1-c]-[1,2,4]*triazine*-6-*carboxylate* (25). The hydrazone (10) (1.0 g) was heated under reflux in ethanol (10 ml) and acetic acid (10 ml) for 3 h. The cooled solution deposited golden crystals of the *methyl triazinecarboxylate acetic acid solvate* (88%) which crystallised from acetic acid with m.p. 250 °C (decomp.) (Found: C, 44.8; H, 4.3. $C_9H_9N_5O_3 \cdot CH_3CO_2H$ requires C, 44.8; H, 4.4%). The acetic acid solvate was decomposed in boiling ethanol (2 h). The unsolvated *methyl triazinecarboxylate* precipitated as a yellow powder, m.p. 250 °C (decomp.) (Found: C, 45.6; H, 4.4; N, 29.4%; M^+, 235.081 76. $C_9H_9N_5O_3$ requires C, 45.8; H, 3.8; N, 29.5%; M, 235.081 68). The same unsolvated methyl triazinecarboxylate (85%) was formed when the hydrazone (11) was boiled in ethanol alone.

The methyl triazinecarboxylate formed a *monoacetyl derivative* when it was boiled in acetic anhydride for 0.5 h. The product (75%) crystallised from ethanol–dimethylformamide with m.p. 240—245 °C (decomp.) (Found: C, 47.4; H, 4.1%; M^+, 277.080 97. $C_{11}H_{11}N_5O_4$ requires C, 47.4; H, 4.1%; M, 277.080 83).

Ethyl 3-*carbamoyl*-4,7-*dihydro*-7-*methyleneimidazo*[5,1-c]-[1,2,4]*triazine*-6-*carboxylate* (26). A solution of the hydrazone (11) (1.0 g) was boiled in ethanol (10 ml) and acetic acid (10 ml) for 4 h. The cooled mixture deposited yellow crystals of the *ethyl triazinecarboxylate* (0.8 g), m.p. 270 °C (decomp.) from ethanol–acetic acid (Found: C, 47.7; H, 4.4; N, 27.7%; M^+, 249.086 183. $C_{10}H_{11}N_5O_3$ requires C, 48.2; H, 4.4; N, 28.1%; M, 249.086 75). From the acidic filtrate orange crystals of the covalent *ethanol solvate* of imidazotriazine (26) were obtained. The solvate had m.p. 175 °C (with resolidification), finally melts at 245 °C (decomp.) (Found: C, 46.3; H, 6.3; N, 23.1%;

M^+, 295.128 045. $C_{12}H_{17}N_5O_4.H_2O$ requires C, 46.0; H, 6.1; N, 22.5%; *M*, 295.127 47).

6-*Acetyl*-3-*carbamoyl*-4,7-*dihydro*-7-*methyleneimidazo*[5,1-c][1,2,4]*triazine* (27). Cyclisation of the hydrazone (12) in boiling acetic acid and ethanol as above yielded the *acetyltriazine* (85%), m.p. 250 °C (decomp.) from acetic acid–ethanol [lit.,[7] m.p. 226—227 °C for the compound claimed to be (22)] (Found: C, 49.2; H, 4.3%; M^+, 219. $C_9H_9N_5O_2$ requires C, 49.3; H, 4.1%; *M*, 219).

6-*Benzoyl*-3-*carbamoyl*-4,7-*dihydro*-7-*methyleneimidazo*-[5,1-c][1,2,4]*triazine* (28).—When the hydrazone (13) was boiled in acetic acid and ethanol for 12 h crystals of the yellow *benzoyltriazine* (65%) were deposited when the mixture was diluted with water. The pure product had m.p. 260—265 °C (decomp.) from acetic acid–ethanol (Found: C, 58.3; H, 5.0%; M^+, 281.091 268. $C_{14}H_{11}N_5O_2.H_2O$ requires C, 57.9; H, 4.5%; *M*, 281.091 51).

Ethyl 3-*carbamoyl*-4,7-*dihydro*-7-*ethoxycarbonylmethyleneimidazo*[5,1-c][1,2,4]*triazine*-6-*carboxylate* (29). A solution of the hydrazone (14) (1.0 g) in boiling acetic acid deposited a yellow microcrystalline solid (0.75 g) after 48 h. The *imidazotriazine* had m.p. 220 °C (decomp.) (Found: C, 46.1; H, 5.1%; M^+, 321.107 31. $C_{13}H_{15}N_5O_5{\cdot}H_2O$ requires C, 46.0; H, 5.0%; *M*, 321.106 87).

Methyl 3-*carbamoyl*-1H-7-*methylpyrazolo*[4,3-c]*pyridazine*-6-*carboxylate* (35). A solution of the hydrazone (32) (1.0 g) in ethanol was refluxed for 2 h and cooled. The precipitated pyrazolopyridazine (0.7 g), when crystallised from ethyl acetate, had m.p. 250 °C (decomp.) (Found: C, 45.4; H, 4.05; N, 29.7%; M^+, 235. $C_9H_8N_5O_3$ requires C, 45.8; H, 3.8; N, 29.6%; *M*, 235).

Ethyl 3-*carbamoyl*-1H-7-*methylpyrazolo*[4,3-c]*pyridazine*-6-*carboxylate* (36). This *pyrazolopyridazine* (90%), similarly prepared from hydrazone (33) in boiling ethanol, had m.p. 250 °C (decomp.) (Found: C, 48.2; H, 4.8; N, 28.3%; M^+, 249. $C_{10}H_{10}N_5O_3$ requires C, 48.0; H, 4.8; N, 28.0%; *M*, 249).

3-*Carbamoyl*-6-*cyano*-1H-*pyrazolo*[4,3-c]*pyridazine*-7(4H)-*one* (37). To hydrazone (34) (1.0 g) was boiled in 70% aqueous ethanol for 8 h. The cooled solution deposited crystals of the *pyrazolopyridazinone* (0.8 g), m.p. 250 °C (decomp.) (Found: C, 36.1; H, 2.9%; M^+, 204. $C_7H_4N_6O_2.1.5H_2O$ requires C, 36.4; H, 3.0%; *M*, 204).

Base-catalysed Cyclisations of Hydrazones.—3-*Carbamoyl*-6-*cyanoimidazo*[5,1-c][1,2,4]*triazin*-7(4H)-*one* (38). A solution of the hydrazone (6) (1.0 g) in pyridine (10 ml) and ethanol (15 ml) was boiled (1.5 h). The precipitated yellow solid was collected, crystallised from dimethylformamide–ethanol, and afforded the *triazinone* (0.8 g), m.p. >300 °C (decomp.) (Found: C, 41.3; H, 2.2; N, 41.2%; M^+, 204. $C_7H_4N_6O_2$ requires C, 41.2; H, 2.0; N, 41.2%; *M*, 204).

6-*Benzoyl*-3-*carbamoylimidazo*[5,1-c][1,2,4]*triazin*-7(4H)-*one* (39). A solution of the hydrazone (9) (1.0 g) in 1% alcoholic potassium hydroxide was stirred (5 h) and the mixture was acidified with 1N-hydrochloric acid. The precipitated benzoyltriazinone (85%) crystallised from dimethylformamide–ethanol with m.p. >300 °C (lit.,[8] m.p. >250 °C). The same triazinone (55%) was obtained from the hydrazone (9) in boiling ethanolic pyridine.

6-*Acetyl*-3-*carbamoylimidazo*[5,1-c][1,2,4]*triazin*-7(4H)-one (40). The hydrazone (10) (1.0 g) was stirred in 1% alcoholic potassium hydroxide for 5 h. The precipitated yellow solid (0.8 g) was acidified with 1N-hydrochloric acid and crystallised from dimethylformamide–ethanol mixture. The pure *triazinone* had m.p. >300 °C (decomp.) (Found: C, 41.8; H, 3.55; N, 29.9%; M^+, 221. $C_8H_7N_5O_3{\cdot}0.5H_2O$ requires C, 41.7; H, 3.5; N, 30.4%; *M*, 221). The same triazinone (45%) was prepared by boiling hydrazone (10) in 50% ethanolic pyridine for 2 h; or from the hydrazone (11) and 1% alcoholic potassium hydroxide (as above) in 70% yield; or from the hydrazone (11) in boiling ethanolic pyridine (50% yield).

Ethyl 2-{3-*carbamoyl*-4,7-*dihydro*-7-*oxoimidazo*[5,1-c][1,2,-4]*triazin*-6-*carbonyl*}*acetate* (41). The hydrazone (14) (1.0 g) was stirred in 1% ethanolic potassium hydroxide (25 ml) for 5 h, and the solution was then acidified with 1N-hydrochloric acid. The precipitated *imidazotriazine* (95%) crystallised from dimethylformamide–ethanol with m.p. 320 °C (decomp.) (Found: C, 44.0; H, 4.1; N, 23.3%; M^+, 293.076 011. $C_{11}H_{11}N_5O_5{\cdot}0.5H_2O$ requires C, 43.7; H, 3.9; N, 23.1%; *M*, 293.075 74).

3-*Carbamoyl*-6-*ethoxycarbonylimidazo*[5,1-c][1,2,4]*triazin*-7(4H)-*one* (42). The hydrazine (15) (1.0 g) was stirred in 1% alcoholic potassium hydroxide (20 ml) for 10 min. Acidification of the mixture with 1N-hydrochloric acid liberated the *triazinone* (70%), m.p. 280 °C (decomp.) (from aqueous ethanol) (Found: C, 39.8; H, 4.1; N, 26.4%; M^+, 251. $C_9H_9N_5O_4{\cdot}H_2O$ requires C, 40.1; H, 4.1; N, 26.0%; *M*, 251).

A solution of the triazinone in 5% aqueous sodium hydrogen carbonate rapidly deposited cream crystals of the *sodium salt* (46), m.p. >350 °C (Found: C, 36.7; H, 3.5; N, 23.6. $C_9H_8N_5NaO_4{\cdot}H_2O$ requires C, 36.9; H, 3.7; N, 23.9%).

Hydrolysis of Imidazo[5,1-c][1,2,4]*triazines.*—(i) Hydrolysis of the aminotriazine (16) (0.4 g) in refluxing 2N-hydrochloric acid (0.5 h) yielded a cream solid (0.35 g) when cooled. The product was identical (i.r.) to a sample of the hydrate of the triazinone (42) prepared by base-catalysed cyclisation of hydrazone (15) (see above).

(ii) 3-Carbamoyl-6-ethoxycarbonylimidazo[5,1-c][1,2,4]-triazin-7(4*H*)-one hydrate (0.4 g) was stirred in 5N-sodium, hydroxide for 0.5 h. The precipitated solid was collected, acidified with 1N-hydrochloric acid, and the crude product (0.3 g) crystallised from aqueous ethanol to afford 3-*carbamoyl*-4,7-*dihydro*-7-*oxoimidazo*[5,1-c][1,2,4]*triazin*-6-*carboxylic acid* (43), m.p. 265—270 °C (efferv.) (Found: C, 34.7; H, 2.9; N, 29.4%; M^+, 179. $C_7H_5N_5O_4{\cdot}H_2O$ requires C, 34.8; H, 2.9; N, 29.0%; *M*, 223—44 [CO_2]).

(iii) 3-Carbamoyl-6-cyanoimidazo[5,1-c][1,2,4]triazin-7(4*H*)-one (38) (0.5 g) was boiled in polyphosphoric acid (3 ml) for 4 h. The cooled, diluted solution was neutralised with sodium carbonate and the yellow product collected (0.4 g). Crystallisation from dimethylformamide–ethanol afforded 3,6-*dicarbamoylimidazo*[5,1-c][1,2,4]*triazin*-7(4H)-*one* (44), m.p. 340—345 °C (decomp.) (Found: N, 36.3%; M^+, 222. $C_7H_6N_6O_3$ requires N, 36.5%; *M*, 222).

Reactions of Ethyl 7-*Amino*-3-*carbamoylimidazo*[5,1-c]-[1,2,4]*triazine*-6-*carboxylate and Secondary Heteroalicyclic Amines.*—(i) The aminoester (16) (0.5 g) and piperidine (3 ml) were refluxed in benzene (20 ml) for 16 h. The yellow product crystallised from dimethylformamide–ethanol to yield the *piperidino-amide* (49) (0.38 g), m.p. 290 °C (decomp.) (Found: C, 49.5; H, 5.3; N, 33.6%; M^+, 289.128 71. $C_{12}H_{15}N_7O_2$ requires C, 49.8; H, 5.2; N, 33.9%; *M*, 289.127 93).

(ii) The *pyrrolidino-amide* (50) (89%), similarly prepared from the amino-ester (16) and pyrrolidine had m.p. 280 °C (decomp.) (Found: C, 46.1; H, 4.6; N, 34.2%; M^+,

275.113 06. $C_{11}H_{13}N_7O_2 \cdot 0.5H_2O$ requires C, 46.4; H, 4.9; N, 34.5%; *M*, 275.112 65).

(iii) The *morpholino-amide* (51) was similarly prepared from the amino-ester (16) and morpholine in refluxing benzene (70% yield). The product crystallised from dimethylformamide–ethanol with m.p. 280 °C (decomp.) (Found: C, 45.1; H, 4.5; N, 33.6%; M^+, 291.107 98. $C_{11}H_{13}N_7O_3$ requires C, 45.4; H, 4.5; N, 33.6%; *M*, 291.108 83).

(iv) Interaction of the amino-ester (16) and *N*-methylpiperazine furnished the *N-methylpiperazino-amide* (52) (82%), m.p. 285 °C (decomp.) from dimethylformamide–ethanol (Found: C, 47.4; H, 5.5; N, 36.4%; M^+, 304.139 61. $C_{12}H_{16}N_8O_2$ requires C, 47.4; H, 5.3; N, 36.8%; *M*, 304.140 31).

6-Amino-3-carbamoylpyrimido[4,5-e]*imidazo*[5,1-c][1,2,4]-*triazine* (53). A solution of 7-amino-3-carbamoyl-6-cyanoimidazo[5,1-*c*][1,2,4]triazine (17) (0.5 g) in refluxing formamide (5 ml) deposited brown crystals (0.37 g) when the mixture was cooled after 1.5 h. The *pyrimidoimidazotriazine*, when purified by vacuum sublimation, had m.p. >350 °C (decomp.) (Found: C, 41.3; H, 2.7; N, 48.0%; M^+, 230.066 45. $C_8H_6N_8O$ requires C, 41.7; H, 2.6; N, 48.7%; *M*, 230.066 3).

6,8-Diamino-3-carbamoylpyrimido[4,5-e]*imidazo*[5,1-c][1,-2,4]*triazine* (54). Guanidine hydrochloride (5.2 g) was dissolved in sodium ethoxide [prepared from sodium (1.3 g) in absolute ethanol (40 ml)]. Sodium chloride was removed and 7-amino-3-carbamoyl-6-cyanoimidazo[5,1-*c*][1,2,4]triazine (17) (0.6 g) added to the filtrate. Ethanol was volatilised from the mixture and the residue heated at 180 °C for 2 h. The cooled solid was sublimed under reduced pressure to yield the *pyrimidoimidazotriazine* (0.36 g), m.p. 350 °C (decomp.) (Found: N, 51.4; M^+, 245.077 35. $C_8H_7N_9O$ requires N, 51.0%; *M*, 245.077 55).

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