Bicyclic Heterocycles with Nitrogen at the Ring Junction. Part 2.[1] Application of the Dakin–West Reaction to the Synthesis of Imidazo-[5,1-*f*]-1,2,4-triazin-4(3*H*)-ones

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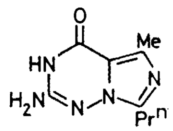
A series of novel acylamino α-keto-esters (4) have been prepared *via* a Dakin–West reaction of acylated α-amino-acids and ethyl oxalyl chloride. Their use in a general synthesis of imidazo[5,1-*f*]-1,2,4-triazin-4(3*H*)-ones (7) is described. The conversion of the imidazotriazinones into the corresponding imidazo[5,1-*f*]-1,2,4-triazines (20) and their 3,4-dihydro-derivatives (19) are also reported.

RECENTLY we described the synthesis and chemistry of 2-amino-5-methyl-7-propylimidazo[5,1-*f*]-1,2,4-triazin-4(3*H*)-one (1) and the corresponding imidazotriazine derivative (2).[1] We now report an improved procedure that allows a more flexible approach to the preparation of a wide range of compounds based on the imidazo[5,1-*f*]-1,2,4-triazine ring system.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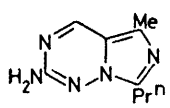
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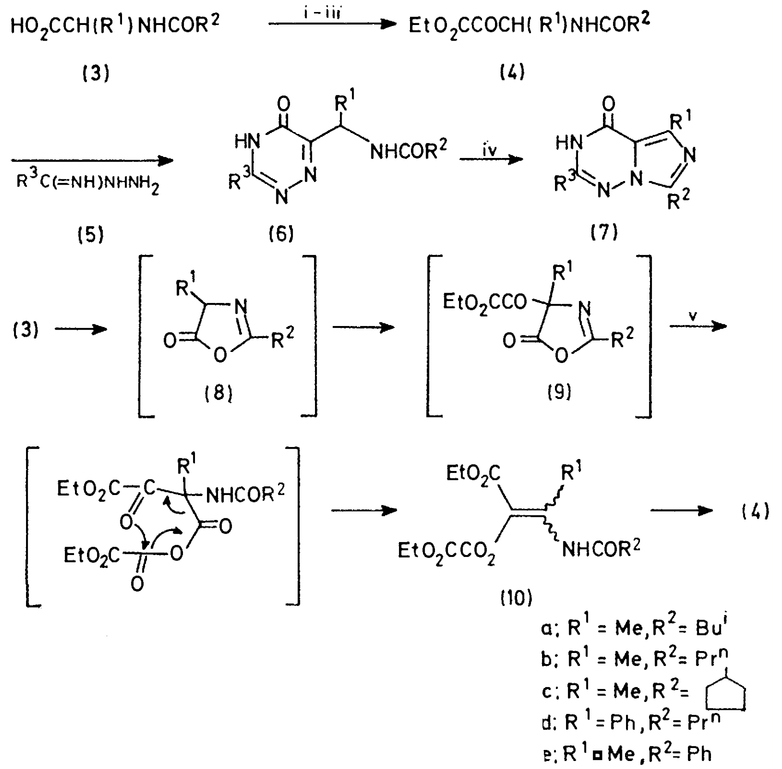
The principal feature of this new method is the condensation of an acylamino-α-keto-ester (4) with an amidrazone or aminoguanidine derivative (5) to afford the key intermediate (6).[1] Although the formation of an acylamino α-keto-acid has been reported,[2] no general synthetic route to acylamino-α-keto-esters (4) had previously been described. However, we found that these compounds could be obtained from α-amino-acids and ethyl oxalyl chloride *via* the Dakin–West reaction.[3] Treatment of the appropriate acylamino-acid (3) with ethyl oxalyl chloride (2 equiv.), pyridine (3 equiv.), and a catalytic quantity of 4-dimethylaminopyridine (DMAP),[4] gave the enol esters (10) which were hydrolysed directly with base to the acylamino-α-keto-ester (4). In general the crude enol esters (10a—d) were isolated as oils but the benzamido-derivative (10e) was obtained as a stable crystalline solid.

The azlactones (8) were shown to be intermediates in the reaction by the independent synthesis of (8b) and subsequent treatment with ethyl oxalyl chloride (1

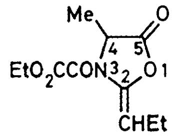


SCHEME Reagents: i, EtO_2CCOCl–pyridine–DMAP; ii, H_2O; iii, base; iv, polyphosphoric acid; v, $EtO_2CCO_2^-$

equiv.), pyridine (2 equiv.), and monoethyl oxalate (1 equiv.) in refluxing tetrahydrofuran to give the enol ester (10b). This process presumably involves the *C*-acylated oxazolone (9b) but the latter could not be isolated under the conditions of the reaction. Support for this type of *C*-acylated intermediate is provided by the work of Steglich and Höfle who have reported [5] the preparation of (9e) by acylation of 4-methyl-2-phenyloxazolin-5-one (8e) with ethyl oxalyl chloride in the presence of triethylamine at 0 °C. The enol ester (10b) was also shown to contain the *N*-acyloxazolone (11) as an impurity. The structure of this by-product was assigned on the basis of its n.m.r. and mass spectra and by hydrogenation to give a mixture of oxazolidinones (12) and (13). The *N*-acyloxazolone (11) was the major product when reaction of the oxazolone (8b) with ethyl oxalyl chloride (1 equiv.) and pyridine (2 equiv.) was carried out in tetrahydrofuran at reflux *in the absence of monoethyl oxalate*. This implies that monoethyl oxalate is required in the reaction for the formation of the enol esters (10).

The α-keto-esters ethyl 3-butyramido-2-oxobutyrate (4b) and ethyl 3-isovaleramido-2-oxobutyrate (4a) were characterised, after chromatography, as low melting crystalline solids but in most cases these intermediates were used in subsequent reactions without purification.

Condensation of aminoguanidine (5; $R^3 = NH_2$) with the α-keto-ester (4b) afforded the triazinone (6; R^1 = Me, R^2 = Pr, $R^3 = NH_2$) in 50% yield which on cyclisation with polyphosphoric acid gave the imidazotriazinone (1), previously described.[1] By employing amidrazones in place of aminoguanidine in the above sequence we have



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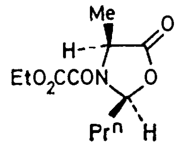

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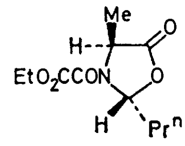

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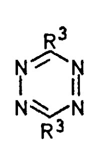

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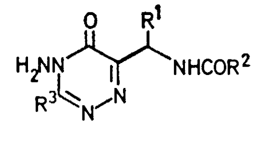

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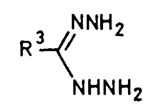

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been able to introduce alkyl, benzyl, and phenyl substituents at the 2-position of the imidazo[5,1-*f*]-1,2,4-triazine nucleus. In most cases it was found convenient to generate the amidrazone (5; R^3 = alkyl or benzyl) *in situ* from the appropriate amidine,[6] and then carry out the condensation reaction with the α-keto-ester at 70—80° in ethanol. Analytical and spectral data for the

TABLE 1

Preparation of 1,2,4-triazin-5(4*H*)-ones (6) from amidrazones and acylamino-α-keto-esters

Compound	R^1	R^2	R^3	M.p. (°C) (Recryst. solvent)	Yield * (%)	Found (%) C	H	N	Molecular formula	Required (%) C	H	N
(6a)	Me	Bu^i	Me	224—226 (EtOH)	20	52.2	7.8	23.45	$C_{11}H_{18}N_4O_2$	55.45	7.6	23.5
(6b)	Me	Bu^i	Pr^i	203—205 (EtOAc)	18	58.45	8.45	21.05	$C_{13}H_{22}N_4O_2$	58.6	8.35	21.05
(6c)	Me	Bu^i	Ph	236—238 (EtOH)	21	64.0	6.8	18.7	$C_{16}H_{20}N_4O_2$	64.0	6.7	18.65
(6d)	Me	Pr^n	Me	235—237 (EtOH)	18	53.15	7.4	24.75	$C_{10}H_{16}N_4O_2$	53.55	7.2	25.0
(6e)	Me	Bu^i	H	167—169 (EtOH–EtOAc)	13	45.65	6.35	21.3	$C_{10}H_{16}N_4O_2\cdot$HCl	46.05	6.55	21.5
(6f)	Me	Pr^n	Et	174—177 (EtOH)	15	54.95	7.55	23.55	$C_{11}H_{18}N_4O_2$	55.45	7.6	23.5
(6g)	Me	Pr^n	$PhCH_2CH_2$	201—202 (EtOH)	27	64.95	6.8	17.95	$C_{17}H_{22}N_4O_2$	64.95	7.05	17.8
(6h)	Me	Pr^n	$PhCH_2$	176—177 (EtOH)	17	64.1	6.6	18.6	$C_{16}H_{20}N_4O_2$	64.0	6.7	18.65
(6i)	Me	Bu^i	$PhCH_2$	190—193 (EtOH–EtOAc)	17	64.65	7.05	17.8	$C_{17}H_{22}N_4O_2$	64.95	7.05	17.8
(6j)	Ph	Pr^n	Me	210—212 (EtOAc)	17	63.2	6.35	19.5	$C_{15}H_{18}N_4O_2$	62.9	6.35	19.55
(6k)	Me	cyclo-C_5H_9	Me	211—214 (EtOAc)	20	57.45	7.45	22.8	$C_{12}H_{18}N_4O_2$	57.6	7.25	22.4
(6l)	Me	Ph	Me	201—204 (EtOH–EtOAc)	26	60.5	5.35	21.55	$C_{13}H_{14}N_4O_2$	60.45	5.45	21.7

* Yield of base from amidine.

TABLE 2

Preparation of imidazo[5,1-*f*]-1,2,4-triazinones (7) from 1,2,4-triazin-5(4*H*)-ones (6)

Compound	R^1	R^2	R^3	M.p. (°C) (Recryst. solvent)	Yield (%)	Found (%) C	H	N	Molecular formula	Required (%) C	H	N
(7a)	Me	Bu^i	Me	186—188 (EtOAc)	63	59.75	7.25	25.3	$C_{11}H_{16}N_4O$	60.0	7.3	25.45
(7b)	Me	Bu^i	Pr^i	135—137 (Et_2O)	57	62.55	8.2	22.35	$C_{13}H_{20}N_4O$	62.85	8.1	22.55
(7c)	Me	Bu^i	Ph	253—255 (EtOAc)	62	67.6	6.2	19.75	$C_{16}H_{18}N_4O$	68.05	6.45	19.85
(7d)	Me	Pr^n	Me	232—235 (EtOAc)	75	58.45	6.75	27.25	$C_{10}H_{14}N_4O$	58.25	6.85	27.15
(7e)	Me	Bu^i	H	229—231 (EtOAc–Et_2O)	32	57.95	6.8	27.25	$C_{10}H_{14}N_4O$	58.25	6.85	27.15
(7f)	Me	Pr^n	Et	215—217 (EtOAc)	42	59.75	7.45	25.35	$C_{11}H_{16}N_4O$	60.0	7.3	25.45
(7g)	Me	Pr^n	$PhCH_2CH_2$	159—160 (EtOAc)	74	69.0	6.7	18.75	$C_{17}H_{20}N_4O$	68.9	6.8	18.9
(7h)	Me	Pr^n	$PhCH_2$	156—157 (EtOAc)	85	67.75	6.35	19.8	$C_{16}H_{18}N_4O$	68.05	64.5	19.85
(7i)	Me	Bu^i	$PhCH_2$	164—165 (EtOAc)	67	68.75	6.8	18.85	$C_{17}H_{20}N_4O$	68.9	6.8	18.9
(7j)	Ph	Pr^n	Me	190—191 (EtOAc)	39	66.95	6.0	20.55	$C_{15}H_{16}N_4O$	67.15	6.0	20.9
(7k)	Me	cyclo-C_5H_9	Me	208—210 (EtOAc)	62	62.4	7.05	24.05	$C_{12}H_{16}N_4O$	62.05	6.95	24.1

TABLE 3

Preparation of 3,4-dihydroimidazo[5,1-*f*]-1,2,4-triazines (19) from imidazo[5,1-*f*]-1,2,4-triazin-4(3*H*)-ones (7)

Compound	R[1]	R[2]	R[3]	M.p. (°C) (Recryst. solvent)	Yield (%) ‡	Found (%) C	H	N	Molecular formula	Required (%) C	H	N
(19a)	Me	Bu[i]	Me	145—148 * (Pr[i]OH–Et$_2$O)	83	55.75	7.05	17.3	$C_{15}H_{22}N_4O_4$	55.9	6.9	17.4
(19b)	Me	Bu[i]	Pr[i]	189—194 † (Pr[i]OH–EtOAc)	48	58.0	8.6	21.1	$C_{13}H_{22}N_4$,HCl	57.65	8.55	20.7
(19c)	Me	Bu[i]	Ph	235—239 † (EtOH–EtOAc)	65	63.0	7.0	18.4	$C_{16}H_{20}N_4$,HCl	63.05	6.95	18.4
(19d)	Me	Pr[n]	Me	143—149 (decomp.) (EtOAc)	74	62.75	8.85	29.25	$C_{10}H_{16}N_4$	62.45	8.4	29.15
(19e)	Me	Bu[i]	H	147—149 (Et$_2$O)	18	62.15	8.35	29.0	$C_{10}H_{16}N_4$	62.45	8.4	29.15
(19f)	Me	Pr[n]	Et	115—117 (EtOAc)	31	64.2	8.95	27.2	$C_{11}H_{18}N_4$	64.05	8.8	27.15
(19g)	Me	Pr[n]	PhCH$_2$CH$_2$	115—117 (Et$_2$O)	95	71.95	7.85	19.65	$C_{17}H_{22}N_4$	72.3	7.85	19.85

* Characterised as maleate salt. † Characterised as hydrochloride salt. ‡ Yield of base.

TABLE 4

Preparation of imidazo[5,1-*f*]-1,2,4-triazines (20) from 3,4-dihydroimidazo[5,1-*f*]-1,2,4-triazines (19)

Compound	R[1]	R[2]	R[3]	M.p. (°C) (Recryst. solvent)	Yield (%) §	Found (%) C	H	N	Molecular formula	Required (%) C	H	N
(20a)	Me	Bu[i]	Me	100—103 * (EtOAc–Et$_2$O)	67	53.6	6.55	16.5	$C_{15}H_{20}N_4O_4$,H_2O	53.25	6.55	16.55
(20b)	Me	Bu[i]	Pr[i]	144—146 (decomp.) † (EtOAc–EtOH)	46	54.5	8.55	19.25	$C_{13}H_{20}N_4$,HCl	54.4	8.15	19.25
(20c)	Me	Bu[i]	Ph	117—120 ‡	46	71.8	6.8	20.7	$C_{16}H_{18}N_4$	72.15	6.8	21.05
(20d)	Me	Pr[n]	Me	54—56 ‡	57	62.95	7.55	29.4	$C_{10}H_{14}N_4$	63.15	7.4	29.45

* Characterised as maleate salt. † Characterised as hydrochloride salt. ‡ Purified by sublimation § Yield of base.

TABLE 5

Spectral data for 1,2,4-triazin-5(4*H*)-ones (6)

Compd.	[1]H N.m.r. spectra (τ) ([$^2H_6$]-DMSO) R[1]	R[2]	R[3]	C*H*R[1]	$\nu_{max.}$(Nujol)/cm^{-1}	$\lambda_{max.}$ (EtOH)/nm	ε	$\lambda_{max.}$ (EtOH + NaOH)/nm
(6a)	8.70 (3 H, d)	7.8—8.3 (3 H, m)	7.68 (3 H, s)	4.90 (1 H, m)	1 663	235	9 350	
		9.1 (6 H, d)			1 640	261sh	5 400	
(6b)	8.52 (3 H, d)	7.5—8.0 (3 H, m)	6.85 (1 H, m)	4.52 (1 H, m)	1 635 †	235	9 350	
		9.1 (6 H, d)	8.68 (6 H, d)			260sh	5 400	
(6c)	8.60 (3 H, d)	7.7—8.2 (3 H, m)	1.7—2.0 (2 H, m)	4.8 (1 H, m)	1 630			
		9.1 (6 H, d)	2.2—2.5 (3 H, m)					
(6d)	8.1—8.9 (5 H, m)		7.65 (3 H, s)	4.92 (1 H, m)	1 665	235	9 200	233
		7.85 (2 H, t)			1 642	265sh	5 200	283
		9.1 (3 H, t)						
(6e) *	8.54 (3 H, d)	7.7—8.3 (3 H, m)	1.02 (1 H, s)	4.84 (1 H, q)	1 650	239	9 350	
		9.1 (6 H, d)				263sh	5 200	
(6f)	8.65 (3 H, d)	7.80 (2 H, t)	7.35 (2 H, q)	4.90 (1 H, m)	1 660	236	9 180	
		~8.4 (2 H, m)	8.75 (3 H, t)		1 640	260sh	5 490	
		9.1 (3 H, t)						
(6g)	8.64 (3 H, d)	7.84 (2 H, t)	2.70 (5 H, s)	4.91 (1 H, m)	1 640 †	235	9 590	
		~8.4 (2 H, m)	~7.0 (4 H, m)			266	5 840	
		9.08 (3 H, t)						
(6h)	8.65 (3 H, d)	7.84 (2 H, t)	2.60 (5 H, s)	4.91 (1 H, m)	1 660	235	9 500	
		8.45 (2 H, m)	6.07 (2 H, s)		1 620	260sh	6 000	
		9.10 (3 H, t)						
(6i)	8.65 (3 H, d)	7.5—8.5 (3 H, m)	2.60 (5 H, s)	4.91 (1 H, m)	1 650	237	9 550	234
		9.1 (6 H, d)	6.10 (2 H, s)		1 620	265sh	6 050	284
(6j)	2.60 (5 H, s)	7.75 (2 H, t)	7.68 (3 H, s)	3.68 (1 H, d)	1 630	234	9 600	233
		~8.4 (2 H, m)				264sh	5 200	286
		9.13 (3 H, t)						
(6k)	8.65 (3 H, d)	7.3 (1 H, m)	7.65 (3 H, s)	4.95 (1 H, m)	1 650	235	8 350	232
		8.0—8.6 (8 H, m)				265sh	5 000	283
(6l)	8.54 (3 H, d)	2.0—2.2 (2 H, m)	7.70 (3 H, s)	4.75 (1 H, m)	1 640	231	18 600	
		2.3—2.6 (3 H, m)				266sh	6 450	

* N.m.r. spectrum of HCl salt recorded in D_2O. † In $CHBr_3$ solution.

TABLE 6

Spectral data for imidazo[5,1-*f*]-1,2,4-triazin-4(3*H*)-ones (7)

Compd.	^{1}H N.m.r. spectra (τ) ($CDCl_3$) R^1	R^2	R^3	$\nu_{max.}$ ($CHBr_3$)/ cm^{-1}	$\lambda_{max.}$ (EtOH)/ nm	ε	$\lambda_{max.}$ (EtOH + NaOH)/ nm
(7a)	7.40 (3 H, s)	7.15 (2 H, d)	7.63 (3 H, s)	1 680	222	24 200	235
		7.8 (1 H, m)		1 645	252	9 000	261
		9.00 (6 H, d)			265sh	6 200	269sh
					281sh		300
(7b)	7.35 (3 H, s)	7.12 (2 H, d)	6.85—7.35 (1 H, m)	1 685	222	23 450	
		7.45—7.95 (1 H, m)	8.60 (6 H, d)	1 635	251	8 850	261
		9.00 (6 H, t)			266sh		270sh
					285sh		297
(7c) *	7.41 (3 H, s)	7.10 (2 H, d)	1.7—1.9 (2 H, m)	1 685	243	23 850	
		~7.7 (1 H, m)	2.15—2.4 (3 H, m)		264sh	19 750	
		8.95 (6 H, d)					
(7d)	7.40 (3 H, s)	7.1 (2 H, t)	7.55 (3 H, s)	1 680	222	24 200	233
		8.2 (2 H, m)		1 648	248	8 700	260
		9.0 (3 H, t)			263sh	6 150	269sh
					280sh	2 400	297
(7e)	7.40 (3 H, s)	7.10 (2 H, d)	2.53br (1 H, s)	1 690	224	23 700	
		7.75 (1 H, m)			247	8 700	258sh
		9.05 (6 H, d)			262sh	5 500	268sh
					285sh		
(7f)	7.38 (3 H, s)	7.05 (2 H, t)	7.30 (2 H, q)	1 680	221	24 200	
		8.20 (2 H, m)	8.60 (3 H, t)		250	8 800	
		8.99 (3 H, t)			278sh	2 700	
(7g)	7.39 (3 H, s)	~6.7—7.2 (2 H, m)	~2.75 (5 H, m)	1 680	218	25 600	
		8.20 (2 H, m)	6.7—7.2 (4 H, m)	1 640	254	9 800	
		9.05 (3 H, t)			265sh		
(7h)	7.35 (3 H, s)	7.0 (2 H, t)	2.5—2.8 (5 H, m)	1 690	221	25 000	
		8.15 (2 H, m)	6.1 (2 H, s)		254	10 100	
		9.00 (3 H, t)			265sh	7 300	
(7i)	7.32 (3 H, s)	7.06 (2 H, d)	2.55 (5 H, m)	1 690	222	25 550	234
		7.7 (1 H, m)	6.1 (2 H, s)		253	10 450	262
		9.0 (6 H, d)			265sh	7 700	270sh
							300
(7j) *	1.50 (2 H, m)	7.07 (2 H, t)	7.75 (3 H, s)	1 680	275	10 200	
	2.3—2.6 (3 H, m)	8.20 (2 H, m)		1 649	295	9 900	
		9.00 (3 H, t)			311	10 100	
(7k)	7.38 (3 H, s)	~6.5 (1 H, m)	7.60 (3 H, s)	1 685	224	23 800	235
		7.7—8.4 (8 H, m)			255	9 050	259
					265	6 250	269sh
							300

* N.m.r. spectrum recorded in [$^2H_6$]DMSO.

TABLE 7

Spectral data for 3,4-dihydroimidazo[5,1-*f*]-1,2,4-triazines (19)

Compound	^{1}H N.m.r. spectra (τ) ($CDCl_3$) R^1	R^2	R^3	4-H	$\lambda_{max.}$/nm	ε
(19a)	7.90 (3 H, s)	7.34 (2 H, d)	7.99 (3 H, s)	5.50br (2 H, s)	253	9 300
		7.6—8.1 (1 H, m)				
		9.02 (6 H, d)				
(19b)	7.90 (3 H, s)	7.3 (2 H, d)	7.3—7.9 (1 H, m)	5.50br (2 H, s)	254	9 550
		7.3—7.9 (1 H, m)	8.75 (6 H, d)			
		9.00 (6 H, d)				
(19c)	7.88 (3 H, s)	7.25 (2 H, d)	2.0—2.3 (2 H, m)	5.35br (2 H, s)	224	15 350
		7.5—8.1 (1 H, m)	2.3—2.7 (3 H, m)		298	9 100
		9.01 (6 H, d)				
(19d)	7.89 (3 H, s)	7.2 (2 H, t)	7.98 (3 H, s)	5.50br (2 H, s)	254	9 200
		8.3 (2 H, m)				
		9.0 (3 H, t)				
(19e)	7.90 (3 H, s)	7.34 (2 H, d)	3.06 (1 H, d)	5.47br (2 H, s)	253	9 000
		7.5—8.2 (1 H, m)				
		9.02 (6 H, d)				
(19f)	7.92 (3 H, s)	7.25 (2 H, t)	7.70 (2 H, q)	5.55br (2 H, s)	253	9 300
		8.3 (2 H, m)	8.80 (3 H, t)			
		9.02 (3 H, t)				
(19g) *	8.02 (3 H, s)	7.3—7.7 (2 H, m)	2.7 (5 H, s)	5.62br (2 H, s)	257	9 950
		8.37 (2 H, m)	7.06 (2 H, m)			
		9.11 (3 H, t)	7.3—7.7 (2 H, m)			

* N.m.r. spectrum in [$^2H_6$]DMSO

TABLE 8

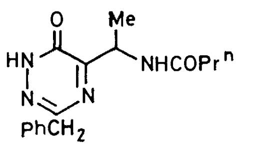
Spectral data for imidazo[5,1-*f*]-1,2,4-triazines (20)

Compound	^{1}H N.m.r. spectra (τ) ($CDCl_3$) R^1	R^2	R^3	4-H		$\lambda_{max.}$/nm	ε
(20a) *	7.61 (3 H, s)	7.10 (2 H, d)	7.80 (3 H, s)		3.76 (1 H, s)	229	17 600
		7.5—8.0 (1 H, m)				250	9 000
		9.00 (6 H, d)				368	
(20b)	7.41 (3 H, s)	7.00 (2 H, d)	6.9 (1 H, m)	1.07 (1 H, s)	3.62 (1 H, s) †	230	9 800 §
		7.7 (1 H, m)	8.65 (6 H, d)			252	8 850
		9.0 (6 H, d)				357	260
(20c)	7.38 (3 H, s)	6.90 (2 H, d)	~1.6 (2 H, m)	0.95 (1 H, s)	3.45 (1 H, s) ‡	228	14 050
		7.6 (1 H, m)	~2.45 (3 H, m)			267	34 050
		9.0 (6 H, d)				275sh	29 550
						280	1 350
(20d)	7.52 (3 H, s)	6.95 (2 H, t)	7.52 (3 H, s)	1.08 (1 H, s)	3.55 (1 H, s) ‡	228	30 950
		8.1 (2 H, m)				261	2 600
		8.95 (3 H, t)				370	2 350

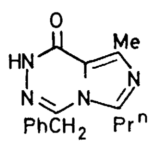
* N.m.r. data is for maleate salt in D_2O; u.v. data for maleate salt in EtOH. † 4-H Chemical shift of HCl salt in D_2O. ‡ 4-H Chemical shift of free base in DCl–D_2O. § U.v. data for HCl salt in EtOH.

1,2,4-triazin-5(4*H*)-ones are compiled in Tables 1 and 5. The magenta tetrazines (14) were a by-product of virtually all the condensation reactions and this may account for the modest yields observed in these reactions. On a few occasions formation of small amounts of N^4-aminotriazinones (15) were also observed, presumably resulting from the condensation of 3-substituted dihydroformazans (16) (generated from further reaction of amidrazones with hydrazine) with the α-keto-esters (4).

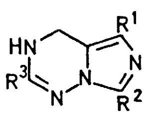
The structure (6) of the triazinones has been confirmed by *X*-ray crystallographic analysis of the subsequently prepared imidazotriazine derivatives (7c) and (19d). However in one instance we did observe the alternative mode of addition when the triazinones (6h) (see Table 1) and (17) were isolated from the reaction of phenyl-



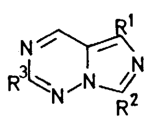
(17)



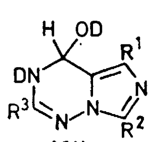
(18)



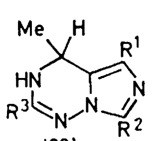
(19)



(20)
a; R^1 = R^3 = Me, R^2 = Bu^i
d; R^1 = R^3 = Me, R^2 = Pr^n



(21)



(22)
a; R^1 = R^3 = Me, R^2 = Bu^i
b; R^1 = R^3 = Me, R^2 = Pr^n

acetamidrazone with the α-keto-ester (4b). A recent communication discloses the formation of both possible triazinones from the condensation of benzamidrazone with diethyl 2-methyl-3-oxosuccinate.[7]

Cyclisation of (6h) (polyphosphoric acid) afforded the imidazotriazinone (7h) in 85% yield whereas under similar conditions the isomeric imidazo[1,5-*d*]-1,2,4-triazin-1(2*H*)-one (18) was formed in only 20% yield from the triazinone (17). In the latter case the low yield is presumably due to an unfavourable steric interaction during ring closure.

Although imidazo[5,1-*f*]-1,2,4-triazin-4(2*H*)-ones (7a—k) were prepared in good yield from the corresponding 1,2,4-triazin-5(4*H*)-ones using polyphosphoric acid as the cyclising agent (Tables 2 and 6), treatment with phosphoryl chloride in refluxing 1,2-dichloroethane was found to be equally effective. Reduction of the carbonyl function of the imidazotriazinones (7) to provide 3,4-dihydroimidazo[5,1-*f*]-1,2,4-triazines (19) was best achieved with lithium aluminium hydride in 1,2-dimethoxyethane at reflux (Tables 3 and 7).

Dehydrogenation of the dihydroimidazotriazines (19a—d) over palladium on charcoal afforded imidazo-[5,1-*f*]-1,2,4-triazines (20a—d) (Table 4). The n.m.r spectra of the protonated imidazotriazines in D_2O revealed a striking upfield shift of the 4-H signal from its position in the free base (Table 8). This can be rationalised in terms of covalent hydration of the 3,4-azomethine bond to give the species (21).[8] As in the case of the imidazotriazine (2) [1] the 3,4-azomethine bond reacted readily with Grignard reagents. Thus, reaction of (20a and d) with methylmagnesium iodide afforded the 3,4-dihydro-4-methylimidazotriazines (22a and b) in good yield (67 and 64%, respectively).

EXPERIMENTAL

The ^{1}H n.m.r. spectra were measured ($SiMe_4$ internal standard) on a Varian EM 390 or a Perkin-Elmer R12A spectrometer, and the i.r. spectra and u.v. spectra (ethanol solutions) were recorded on Perkin-Elmer 357 and 402 spectrophotometers respectively (by Dr. J. H. Hunt and his staff). The mass spectra were recorded on an A.E.I. MS30 spectrometer (by Dr. R. Tanner). The elemental analyses were determined (by Dr. L.R. Rowe and his staff) on a Hewlett–Packard 185B C, H, and N analyser. All m.p.s are uncorrected. Chromatography was carried out on Merck silica gel 60.

Ethyl 3-Butyramido-2-oxobutyrate (4b).—To a stirred solution of butyrylalanine (238.5 g, 1.5 mol), 4-dimethylaminopyridine (6 g, 0.05 mol), and pyridine (355.5 g, 4.5 mol) in tetrahydrofuran (1 l) was added ethyl oxalyl chloride (409.5 g, 3 mol) at a rate sufficient to initiate refluxing. The mixture was then heated to maintain a gentle reflux for 1.5 h. The cooled mixture was treated with water (1 l) and extracted with ethyl acetate (3 × 500 ml). The organic extract was washed with water (2 × 250 ml) and dried over sodium sulphate. Removal of the solvent afforded the enol ester (10b) as an orange syrup (293 g).

A solution of the enol ester (293 g) in absolute ethanol (270 ml) was treated with sodium hydrogencarbonate (66 g) and the mixture heated at reflux for 2.5 h. After the mixture had cooled to room temperature sodium hydrogencarbonate was filtered off and the filtrate was concentrated to an oil. This oil in ethyl acetate solution was filtered and then evaporated *in vacuo* to provide crude ethyl 3-butyramido-2-oxobutyrate (200 g).

Purification of the product could be effected by chromatography on a column of silica gel (cyclohexane–ethyl acetate, 3 : 1 ⟶ 1 : 1), to give a pale yellow viscous oil that crystallised on trituration with pentane–ether at *ca.* 10°. Recrystallisation from pentane–ether gave *ethyl* 3-*butyramido*-2-*oxobutyrate* (4b), m.p. 46.5—49.5°; $\nu_{max.}$ ($CHBr_3$) 3 430, 1 735 (shoulder), 1 730, and 1 665 cm^{-1}; τ ($CDCl_3$) 3.5br (1 H, d, NH), 4.90 (1 H, m, CH), 5.65 (2 H, q, $CO_2CH_2CH_3$), 7.79 (2 H, t, $CH_2CH_2CH_3$), 8.3 (2 H, m, $CH_2CH_2CH_3$), 8.57 (3 H, d, CH_3CH), 8.64 (3 H, t, $CO_2CH_2CH_3$), and 9.07 (3 H, t, $CH_2CH_2CH_3$) (Found: C, 56.1; H, 8.1; N, 6.55. $C_{10}H_{17}NO_4$ requires C, 55.8; H, 7.95; N, 6.5%).

Ethyl 3-*Isovaleramido*-2-*oxobutyrate* (4a).—This was prepared from isovalerylalanine using a similar procedure, m.p. 52—53.5° (from pentane–ether); $\nu_{max.}$ ($CHBr_3$) 3 425, 1 740 (shoulder) 1 730, and 1 665 cm^{-1}; τ ($CDCl_3$) 3.7br (1 H, d, NH), 4.90 (1 H, m, CH), 5.66 (2 H, q, $CO_2CH_2CH_3$), 7.7—8.2 [3 H, m, $CH_2CH(CH_3)_2$], 8.59 (3 H, d, CH_3CH), 8.61 (3 H, t, $CO_2CH_2CH_3$), and 9.06 [6 H, d, $CH_2CH(CH_3)_2$] (Found: C, 57.35; H, 8.65; N, 6.0. $C_{11}H_{19}NO_4$ requires C, 57.6; H, 8.35; N, 6.1%).

Ethyl 3-(N-*Cyclopentylcarboxamide*)-2-*oxobutyrate* (4c).—This was prepared from *N*-cyclopentylcarbonylalanine as above and was obtained as a golden yellow oil and was used directly, without characterisation, in the preparation of triazinone (6k).

Ethyl 3-*Butyramido*-2-*oxo*-3-*phenylpropionate* (4d).—This was prepared from butyryl-α-phenylglycine, as described above, as a golden yellow oil and was used directly, without full characterisation, in the preparation of triazinone (6j); τ ($CDCl_3$) 2.63 (5 H, s, ArH), 3.3br (1 H, m, NH), 3.73 (1 H, d, CHNH), 5.80 (2 H, q, $CO_2CH_2CH_3$), 7.80 (2 H, t, $CH_2CH_2CH_3$), 8.1—8.6 (2 H, m, $CH_2CH_2CH_3$), 8.80 (3 H, t, $CO_2CH_2CH_3$), and 9.10 (3 H, t, $CH_2CH_2CH_3$).

Ethyl 3-*Benzamido*-2-*oxobutyrate* (4e).—To a stirred solution of benzoylalanine (190 g, 1.0 mol), 4-dimethylaminopyridine (4 g, 0.034 mol), and pyridine (237 g, 3.0 mol) in tetrahydrofuran (1 l) was added ethyl oxalyl chloride (273 g, 2.0 mol) at a rate sufficient to initiate refluxing. The mixture was then heated to maintain a gentle reflux for 3.5 h. The cooled mixture was treated with water (1 l) and stirred vigorously at room temperature for 0.5 h. The tetrahydrofuran layer was separated and the aqueous phase was extracted with ethyl acetate (2 × 150 ml). The organic extracts were combined, dried (anhydrous Na_2SO_4), and evaporated *in vacuo* to leave a pale yellow solid. Recrystallisation of this material from ethyl acetate afforded the *enol ester* (10e), as needles (202.5 g, 59%), m.p. 106—108°, $\nu_{max.}$ ($CHBr_3$) 3 300, 1 780, 1 745, 1 690, 1 670, and 1 630 cm^{-1}; $\lambda_{max.}$ (EtOH) 233 (ε 10 600) and 308 nm (11 100); τ ($CDCl_3$) 1.9—2.1 (2 H, m, ArH), 2.3—2.6 (3 H, m, ArH), 5.52 (2 H, q, $CO_2CH_2CH_3$), 5.68 (2 H, q, $CO_2CH_2CH_3$), 7.4 (3 H, s, CCH_3), 8.53 (3 H, t, $CO_2CH_2CH_3$), and 8.68 (3 H, t, $CO_2CH_2CH_3$) (Found: C, 58.4; H, 5.5; N, 3.95. $C_{17}H_{19}NO_7$ requires C, 58.45; H, 5.5; N, 4.0%).

To a stirred suspension of the enol ester (10e) (202.5 g, 0.58 mol) in absolute ethanol (600 ml), at room temperature, was added dropwise a solution of sodium ethoxide in ethanol until a clear yellow solution resulted. The ethanol was then removed *in vacuo* and the residue treated with ether. The ether solution was washed with water, dried (anhydrous Na_2SO_4), and evaporated *in vacuo* to give a yellow oil. Chromatography on a column of silica gel gave *ethyl* 3-*benzamido*-2-*oxobutyrate* as a pale yellow oil. This material was directly used in the preparation of triazinone (6l); $\nu_{max.}$ ($CHBr_3$) 3 420, 1 735, and 1 658 cm^{-1}; τ ($CDCl_3$) 2.2 (2 H, m, ArH), 2.5 (H, m, ArH), 2.8br (1 H, m, NH), 4.70 (1 H, m, CHNH), 5.65 (2 H, q, $CO_2CH_2CH_3$), and 8.4—8.7 (5 H, d + t, CH_3CH, $CH_3CH_2CO_2$).

Preparation of 1,2,4-*Triazin*-5(4H)-*ones* (6).—*General procedure*. To an ice-cold solution of amidine hydrochloride (0.7 mol) in absolute ethanol (600 ml) was added a solution of hydrazine hydrate (0.7 mol) in absolute ethanol (20 ml) over 10 min. The cooling bath was removed and the mixture stirred at room temperature for 5—10 min. A solution of the acylamino α-keto-ester (4) (0.7 mol) in absolute ethanol (100 ml) was then added * and the mixture heated at 70° for 4 h. The mixture was cooled to room temperature and the precipitated ammonium chloride filtered off. The filtrate was concentrated, ethyl acetate added, and the precipitated 1,2,4-triazinone collected by filtration. Concentration of the filtrate provided further crops of product.

N-[1-(3-*Benzyl*-1,6-*dihydro*-6-*oxo*-1,2,4-*triazin*-5-*yl*)*ethyl*]-*butyramide* (17).—This was obtained as an off-white crystalline solid, m.p. 166—168.5°, $\nu_{max.}$ ($CHBr_3$) 3 360, 1 680, and 1 590 cm^{-1}; $\lambda_{max.}$ 225 (ε 12 200), 259 (1 900), 266 (1 950), 271 (3 900), and 306 nm (3 900); τ [$(CD_3)_2SO$] 1.8br (1 H, d, NH), 2.70 (5 H, s, ArH), 4.87 (1 H, m, CHNH), 6.03 (2 H, s, $PhCH_2$), 7.90 (2 H, t, $CH_2CH_2CH_3$), 8.5 (2 H, m, $CH_2CH_2CH_3$), 8.68 (3 H, d, CH_3CH), and 9.14 (3 H, t, $CH_2CH_2CH_3$) (Found: C, 63.9; H, 6.75; N, 18.6. $C_{16}H_{20}N_4O_2$ requires C, 64.0; H, 6.7; N, 18.65%).

Preparation of Imidazo[5,1-f]-1,2,4-*triazin*-4(3H)-*ones* (7).—*General procedure. Method A*. Polyphosphoric acid (130 g) was pre-heated to 150° and the 1,2,4-triazin-5(4*H*)-one (0.067 mol) was added portionwise during 10—15 min with stirring. Following complete dissolution of the added triazinone the mixture was heated at 150° for 45 min. The mixture was allowed to cool to *ca.* 100° and poured into ice–water (*ca.* 500 ml) and the solution was then basified by addition of 2N-sodium carbonate solution. The precipitated *imidazotriazinone* was collected by filtration. Extraction of the filtrate with ethyl acetate provided a further quantity of product.

Method B. The 1,2,4-triazin-5(4*H*)-one (0.007 mol) and phosphorus oxychloride (5 ml) in 1,2-dichloroethane (40 ml)

* In the case of triazinone (6e) this addition was made at −60° over 1.5 h. The mixture was allowed to warm to 0° overnight and then heated at reflux for 1.5 h. Chromatography on a column of silica gel (ethyl acetate–ethanol, 6 : 1) was required to purify the product, which was then characterised as its hydrochloride salt (see Table 1).

were heated at reflux for 2 h. The solvent and excess of phosphorus oxychloride were evaporated *in vacuo* and the residue treated with 2N-sodium carbonate solution (50 ml) and ethyl acetate (50 ml). The mixture was shaken vigorously until all the solid had dissolved. The ethyl acetate layer was separated and the aqueous phase extracted with a further quantity of ethyl acetate (2 × 50 ml). The ethyl acetate extracts were combined, dried (Na_2SO_4), and evaporated to provide the *imidazotriazinone*.

4-*Benzyl*-7-*methyl*-5-*propylimidazo*[1,5-d]-1,2,4-*triazin*-1(2H)-*one* (18).—This had $\nu_{max.}$ ($CHBr_3$) 3 395 and 1 673 cm^{-1}; τ [$CDCl_3$–$(CD_3)_2SO$] 1.3br (1 H, s, NH), 2.5—3.0 (5 H, m, ArH), 5.65 (2 H, s, PhCH_2), 7.17 (2 H, t, $CH_2$$CH_2$-$CH_3$), 7.33 (3 H, s, 7-$CH_3$), 8.25 (2 H, m, $CH_2CH_2CH_3$), and 9.08 (3 H, t, $CH_2CH_2CH_3$) (Found: C, 68.0; H, 6.55; N, 19.65. $C_{16}H_{18}N_4O$ requires C, 68.05; H, 6.45; N, 19.85%).

Preparation of 3,4-*Dihydroimidazo*[5,1-f]-1,2,4-*triazines* (19).—*General procedure*. Lithium aluminium hydride (0.145 mol) was added portionwise during 10 min to a stirred solution of the imidazo[5,1-*f*]-1,2,4-triazin-4(3*H*)-one (7) (0.08 mol) in 1,2-dimethoxyethane. The mixture was heated at reflux for 2 h and then cooled and quenched by the sequential addition of water (10 ml), 2N-sodium hydroxide solution (15 ml), and finally water (10 ml) again. The granular precipitate of aluminium salts was filtered off and the filtrate evaporated to leave a partially crystalline residue. Recrystallisation provided pure *dihydroimidazotriazine* (19).

3,4-*Dihydro*-7-*propyl*-2,4,5-*trimethylimidazo*[5,1-f]-1,2,4-*triazine* (22b).—An ethereal solution (90 ml) of methylmagnesium iodide [prepared from methyl iodide (2.84 g, 0.02 mol) and magnesium turnings (0.48 g, 0.02 mol)] was added to a stirred solution of 2,5-dimethyl-7-propylimidazo[5,1-*f*]-1,2,4-triazine (20d) (1.90 g, 0.01 mol) in anhydrous ether (30 ml). The mixture was stirred at room temperature for 15 h and then aqueous NH_4Cl solution was added until all the solid had dissolved. The ether layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 50 ml). The organic extracts were combined, dried (Na_2SO_4), and evaporated to dryness *in vacuo*. The residue was recrystallised from ethyl acetate to afford the *title compound* (1.31 g, 64%), m.p. 175—179°; $\nu_{max.}$ ($CHBr_3$) 3 430 and 1 640 cm^{-1}; $\lambda_{max.}$ 256 nm (ε 10 800); τ ($CDCl_3$) 3.58br (1 H, s, NH), 5.24 (1 H, m, CHNH), 7.27 (2 H, t, $CH_2CH_2CH_3$), 7.89 (3 H, s, 5-CH_3), 8.02 (3 H, s, 2-CH_3), 8.0—8.5 (2 H, m, $CH_2CH_2CH_3$), 8.56 (3 H, d, CH_3CH), and 9.02 (3 H, t, $CH_2CH_2CH_3$) (Found: C, 63.95; H, 8.4; N, 27.6. $C_{11}H_{18}N_4$ requires C, 64.05; H, 8.8; N, 27.15%).

3,4-*Dihydro*-7-*isobutyl*-2,4,5-*trimethylimidazo*[5,1-f]-1,2,4-*triazine* (22a).—This was prepared from the imidazotriazine (20a) (in 67% yield) by a similar procedure to that described for the preparation of (22b), m.p. 174—178° (EtOAc–Et_2O); $\nu_{max.}$ ($CHBr_3$) 3 430 and 1 640 cm^{-1}; $\lambda_{max.}$ 254 nm (ε 9.800); τ ($CDCl_3$) 3.98br (1 H, s, NH), 5.26br (1 H, q, CH_3CHNH), 7.35 (2 H, d, CH_2CHMe$_2$), 7.5—8.2 (1 H, m, CH_2CHMe$_2$), 7.84 (3 H, s, 5-CH_3), 8.00 (3 H, s, 2-CH_3), 8.56 (3 H, d, CH_3CH), and 9.05 (6 H, d, CH_2CHMe$_2$) (Found: C, 65.0; H, 9.2; N, 25.25. $C_{12}H_{20}N_4$ requires C, 65.4; H, 9.15; N, 25.45%).

Preparation of Imidazo[5,1-f]-1,2,4-*triazines* (20).—*General procedure*. The dihydroimidazo[5,1-*f*]-1,2,4-triazine (19) (0.005 mol) and 10% palladium oxide on charcoal (2 g) in *p*-cymene (100 ml) were heated at reflux under nitrogen for 6 h. After cooling to room temperature the catalyst was removed by filtration through Hyflo and the filtrate was extracted with 2N-hydrochloric acid (2 × 75 ml). The aqueous acidic extract was basified with sodium carbonate (to *ca.* pH 8) and extracted with ether (3 × 50 ml). The dried (Na_2SO_4) ethereal extract was evaporated to provide crude *imidazotriazine*. Purification was effected by chromatography on a column of silica gel and elution with ether–ethyl acetate.

4-*Methyl*-2-*propyloxazol*-5(4H)-*one* (8b).—Dicyclohexylcarbodi-imide (22.3 g, 0.108 mol) in dichloromethane (75 ml) was added dropwise over 5 min to a stirred solution of butyrylalanine (17.2 g, 0.108 mol) in dichloromethane (125 ml). The mixture was stirred for 2 h and the precipitated dicyclohexylurea was removed by filtration and washed with dichloromethane (2 × 20 ml). The combined filtrate and washings were concentrated and the crude product was distilled *in vacuo* to give 4-*methyl*-2-*propyloxazol*-5(4H)-*one* as an oil (11.6 g, 76%), b.p. 72—75° at 12 mmHg; $\nu_{max.}$ ($CHBr_3$) 1 820 and 1 670 cm^{-1}; τ ($CDCl_3$) 5.80 (1 H, m, 4-H), 7.52 (2 H, m, $CH_2CH_2CH_3$), 8.25 (2 H, m, $CH_2CH_2CH_3$), 8.55 (3 H, d, 4-CH_3), and 9.00 (3 H, m, $CH_2CH_2CH_3$) (Found: C, 59.15; H, 8.3; N, 10.0. $C_7H_{11}NO_2$ required C, 59.55; H, 7.85; N, 9.9%).

Ethyl 2-(4-*Methyl*-5-*oxo*-2-*propylideneoxazolidin*-3-*yl*)-2-*oxoacetate* (11).—Ethyl oxalyl chloride (1.37 g, 1.12 ml, 0.01 mol) in dry tetrahydrofuran (5 ml) was added dropwise over 5 min to a stirred solution of 4-methyl-2-propyloxazol-5(4*H*)-one (1.4 g, 0.01 mol), 4-dimethylaminopyridine (0.1 g), and dry pyridine (1.6 g, 0.02 mol) in dry tetrahydrofuran (20 ml). The mixture was heated at reflux for 1 h (analytical t.l.c. showed a single product), and then cooled, filtered, and evaporated. The residue was purified by preparative t.l.c., eluting with cyclohexane–ethyl acetate (3 : 1), to give the *title compound* as a pale yellow oil (0.5 g, 20%); $\nu_{max.}$ ($CHBr_3$) 1 820, 1 740, 1 695, and 1 663 cm^{-1}; τ ($CDCl_3$) 4.5br (1 H, olefin CH, sharpens to a triplet at 10°), 5.10 (1 H, q, ring CH), 5.66 (2 H, q, $CO_2CH_2CH_3$), 7.83 (2 H, m, =CHCH_2CH_3), 8.42 (3 H, d, 4-CH_3), 8.61 (3 H, t, $CO_2CH_2CH_3$), and 8.97 (3 H, t, =CHCH_2-CH_3) [Found: M^+, 241.0933. $C_{11}H_{15}NO_5$ requires 241.0950. *m/e*, 116.0384 ($NCOCO_2Et$ + H transfer). $C_4H_6NO_3$ requires *m/e* 116.0347] (Found: C, 55.05; H, 6.4; N, 5.75. $C_{11}H_{15}NO_5$ requires C, 54.75; H, 6.25; N, 5.8%).

Ethyl 2-(4-*Methyl*-5-*oxo*-2-*propyloxazolidin*-3-*yl*)-2-*oxoacetates* (12) *and* (13).—Ethyl 2-(4-methyl-5-oxo-2-propylideneoxazolidin-3-yl)-2-oxoacetate (2.41 g, 0.01 mol) in ethyl acetate (50 ml) was hydrogenated over 10% palladium on charcoal (0.25 g) for 17.5 h (0.01 mol H_2 absorbed). The solution was filtered and evaporated to give an oil (2.4 g). A portion (2 g) was purified by chromatography on a column of silica (50 g); elution with cyclohexane–ethyl acetate (3 : 1) gave the *title compound* as a mixture of isomers (12) and (13) (0.9 g, 44%); $\nu_{max.}$ ($CHBr_3$) 1 800, 1 740, and 1 670 cm^{-1}; τ (DMSO at 105 °C) 3.97 (1 H, m, 2-H, collapsed to 2 s on irradiation of adjacent CH_2), 5.36 (1 H, m, 4-H), 5.65 (2 H, m, CH_3CH_2O), 8.08 (2 H, m, CH_2-CH_2CH_3), 8.44 (3 H, d, CH_3) and 8.48 (3 H, d, CH_3) (both 4-CN_3), 8.64 (5 H, m, CH_3CH_2O + $CH_3CH_2CH_2$), and 9.01 (3 H, m, $CH_3CH_2CH_2$) (Found: C, 53.9; H, 6.8; N, 5.7. $C_{11}H_{17}NO_5$ requires C, 54.3; H, 7.05; N, 5.75%).

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