Bicyclic Pyrimidine Derivatives with a Bridgehead Nitrogen Atom. Part I. Synthesis of *s*-Triazolo[4,3-*a*]pyrimidines

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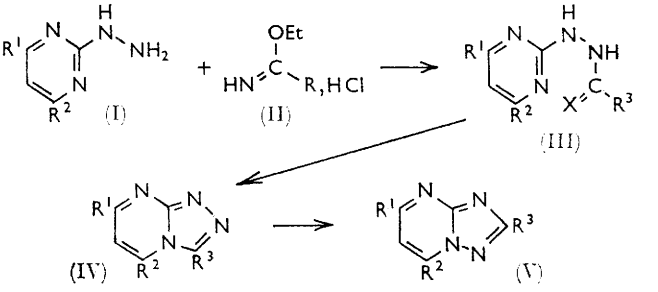
The reaction of 2-hydrazinopyrimidines with ethyl imidate hydrochlorides has been explored as a new route to 3-substituted *s*-triazolo[4,3-*a*]pyrimidines. The synthesis of certain *s*-triazolo[4,3-*a*]pyrimid-7-ones by lead tetra-acetate oxidation of 1-alkyl-2-benzylidenehydrazinopyrimid-6-ones is described. 6-Ethoxycarbonyl-*s*-triazolo[4,3-*a*]pyrimid-7-ones readily isomerise to *s*-triazolo[1,5-*a*]pyrimid-5-ones.

s-TRIAZOLOPYRIMIDINES were required as examples of cyclised aminoguanidines in an extension of earlier work on guanidines and related compounds.[1] The *s*-triazolo[1,5-*a*]pyrimidines are readily obtained [2] from 3-amino-1,2,4-triazoles, however, the preparation of the *s*-triazolo[4,3-*a*]pyrimidines (IV) is often complicated by isomerisation to the *s*-triazolo[1,5-*a*]pyrimidines (V), especially in the presence of acids.[3]

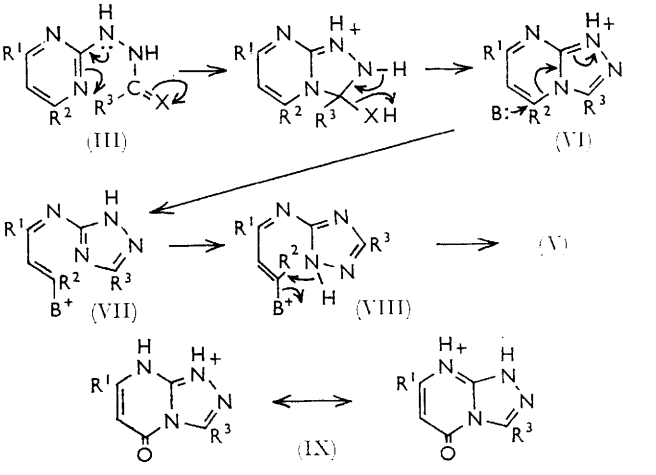
3-Methyl-*s*-triazolo[4,3-*a*]pyrimidines (IV; R^3 = Me) have been prepared [4,5] by cyclisation of 2-hydrazinopyrimidines (I; R^1, R^2 = H, alkyl, or OH) with ethyl orthoacetate. Some 3-methyl derivatives (IV; R^1 or R^2 = OH, R^3 = Me) have also been obtained by cyclisation of the 2-hydrazinopyrimidines (I; R^1 or R^2 = OH) with acetic acid,[6-8] but attempted cyclisation of the 2-hydrazinopyrimidines (I; R^1, R^2 = H or alkyl) with acetic acid gave the hydrazides (III; R^3 = Me, X = O) which could not be cyclised without isomerisation.[9,10] However, the hydrazide (III; R^1 = Me, R^2 = OH, R^3 = CH_2CH_2OH, X = O) cyclised to 5-hydroxy-3-hydroxyethyl-7-methyl-*s*-triazolo[4,3-*a*]-pyrimidine (IV; R^1 = Me, R^2 = OH, R^3 = CH_2CH_2OH) in boiling phenol.[4] 3-Aryl-*s*-triazolo[4,3-*a*]pyrimidines (IV; R^3 = aryl) have been obtained [5,8,11] by lead tetra-acetate oxidation of 2-benzylidenehydrazinopyrimidines, the compound prepared by Allen *et al.*,[12] using this method to cyclise 2-benzylidenehydrazino-4-hydroxy-6-methylpyrimidine in boiling acetic acid is in fact 7-hydroxy-5-methyl-*s*-triazolo[1,5-*a*]pyrimidine and not the triazolo[4,3-*a*]pyrimidine (see refs. 8 and 11).

We have investigated the reaction of ethyl imidate hydrochlorides (II) with 2-hydrazinopyrimidines (I) as an alternative method of preparing 3-substituted *s*-triazolo[4,3-*a*]pyrimidines (IV; R^3 = alkyl or aryl) under mild, neutral conditions, see Scheme 1. The results are summarised in Table 1 and show that the method gives good yields of 5-hydroxy-*s*-triazolo[4,3-*a*]-pyrimidines (IV; R^1 = H, alkyl or aryl, R^2 = OH, R^3 = alkyl or aryl). However, the 2-hydrazinopyrimidines (I; R^1 = R^2 = H or Me) reacted with ethyl imidate hydrochlorides (II) to give the isomeric *s*-triazolo[1,5-*a*]pyrimidines (V; R^1 = R^2 = H, R^3 = Me, CH_2CO_2Et or CH_2CONMe_2) and in one case the intermediate amidrazone (III; R^1 = R^2 = R^3 = Me,



Scheme 1

X = NH_2^+) was the only product isolated. The failure of the amidrazones or hydrazides (III; R^1 = R^2 = H



Scheme 2

or alkyl, X = NH_2^+ or O) to cyclise without isomerisation reflects the susceptibility of the intermediate

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[1] G. J. Durant, G. M. Smith, R. G. W. Spickett, and S. H. B. Wright, *J. Medicin. Chem.*, 1966, **9**, 22.
[2] Following Paper and references therein.
[3] C. F. H. Allen, H. R. Beilfuss, D. M. Burness, G. A. Reynolds, T. F. Tinker, and J. A. Van Allan, *J. Org. Chem.*, 1959, **24**, 787.
[4] C. F. H. Allen, H. R. Beilfuss, D. M. Burness, G. A. Reynolds, T. F. Tinker, and J. A. Van Allan, *J. Org. Chem.*, 1959, **24**, 793.
[5] L. A. Williams, *J. Chem. Soc.*, 1960, 1829.
[6] K. Shirakawa, *J. Pharm. Soc. Japan*, 1959, **79**, 899 (*Chem. Abs.*, 1960, **54**, 556).
[7] K. Shirakawa, *J. Pharm. Soc. Japan*, 1959, **79**, 1487 (*Chem. Abs.*, 1960, **54**, 11,039).
[8] K. Shirakawa, *J. Pharm. Soc. Japan*, 1960, **80**, 956 (*Chem. Abs.*, 1960, **54**, 24,761).
[9] K. Shirakawa, *J. Pharm. Soc. Japan*, 1959, **79**, 903 (*Chem. Abs.*, 1960, **54**, 556).
[10] K. Shirakawa, *J. Pharm. Soc. Japan*, 1959, **79**, 1482 (*Chem. Abs.*, 1960, **54**, 11,039).
[11] J. D. Bower and F. P. Doyle, *J. Chem. Soc.*, 1957, 727.
[12] C. F. Allen, G. A. Reynolds, J. F. Tinker, and L. A. Williams, *J. Org. Chem.*, 1960, **25**, 361.

(VI; R^1, R^2 = H or alkyl) to ring opening, thereby causing rearrangement (Scheme 2). When R^2 = OH this intermediate (IX) is stabilised by amidinium resonance.

The above methods give 5-hydroxy-*s*-triazolo[4,3-*a*]-pyrimidines. Substituted 2-hydrazinopyrimid-6-ones (XI; R^1 = Et or $PhCH_2$, R^2 = $NHNH_2$) have been cyclised to 8-substituted *s*-triazolo[4,3-*a*]pyrimid-7-ones (XII), but an attempt to prepare 7-hydroxy-*s*-triazolo[4,3-*a*]pyrimidine by debenzylation of 8-benzyl-*s*-triazolo[4,3-*a*]pyrimid-7-one (XIIg) failed.

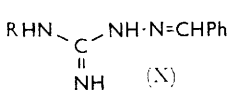
TABLE 1

Products from the reaction of ethyl imidate hydrochlorides (II) with 2-hydrazinopyrimidines (I)

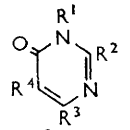
Substituents (I; R^1 R^2) (II; R)	Sol-vent [a]	(IV) Yield (%)	(IV) M. p.	(V) Yield (%)	(V) M. p.	Cryst. from [a]	Found (%) C	H	N	Formula	Required (%) C	H	N
(a) H OH Ph	E	30	210—211°			E	62·05	4·15	26·15	$C_{11}H_8N_4O$	62·25	4·0	26·4
(b) Me OH Ph	E	46	⩽300 [b]	*c*		E	63·55	4·3	25·0	$C_{12}H_{10}N_4O$	63·7	4·45	24·75
	G	60	⩽300										
(c) Ph OH $PhCH_2$	G	69	244—246			B	71·25	4·4	18·35	$C_{18}H_{14}N_4O$	71·5	4·65	18·55
(d) Me OH Me	E	80	312—314 [d]				51·55	5·05	34·0	$C_6H_8N_4O$	51·2	4·9	34·15
(e) H H Me	E			22	126—128 [e]	IP							
					207—208 (HCl)	I	42·45	4·2	32·85	$C_6H_6N_4$,HCl	42·3	4·15	32·85
(f) Me Me Me	E	*f*		*f*	227—230 (HCl)	IP	44·75	6·8	32·15	$C_8H_{13}N_5$,HCl	44·55	6·55	32·45
(g) H H CH_2CO_2Et	E			45	108—110	CP	52·35	5·0	27·4	$C_9H_{10}N_4O_2$	52·4	4·9	27·2
(h) H H CH_2CONMe_2	E			9	141—143·5	CP	52·4	5·55	34·2	$C_9H_{11}N_5O$	52·65	5·4	34·15

[a] E = Ethanol, B = n-butanol, I = isopropyl alcohol, IP = isopropyl alcohol–light petroleum, CP = chloroform–light petroleum, G = ethyleneglycol. [b] Lit.,[3] m. p. ⩽300°. [c] A 4% yield of (V) also obtained. [d] Lit.,[4] m. p. 308—310°. [e] Lit.,[9] m. p. 131—133°. Amidrazone (III; R^1 = R^2 = R^3 = Me, X = NH_2^+) obtained.

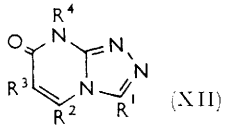
The intermediate 1-substituted 2-hydrazinopyrimid-6-ones (XI; R^2 = $NHNH_2$) could only be obtained in poor yield from 2-methylmercaptopyrimid-6-ones (XI; R^2 = SMe) and hydrazine hydrate following literature



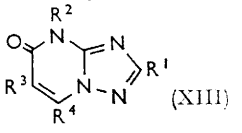
(X)



(XI)



(XII)



(XIII)

procedures.[8,12,13] The benzylidene derivatives (XI; R^2 = NHN=CHPh) could be obtained in good yield, however, by condensation of β-keto-esters with *N*-alkyl-*N'*-benzylideneaminoguanidines (X). The 1-benzyl-2-benzylidenehydrazino-4-methylpyrimid-6-one (XIf) prepared by this method was identical with an authentic sample prepared by the method of Shirakawa.[8] 2-Benzylidenehydrazino-1,4-dimethylpyrimid-6-one (XIe) was prepared by condensation of benzaldehyde with the known 2-hydrazinopyrimid-6-one (XI; R^1 = R^3 = Me, R^2 = $NHNH_2$, R^4 = H).[12] Comparison of the u.v. spectra (Table 2) of these compounds (XIe and f) with the compounds prepared from *N*-alkyl-*N'*-benzylideneaminoguanidines confirmed that all the compounds had the 1-alkyl-2-benzylidenehydrazinopyrimid-6-one structure.

The benzylidene derivatives (XIa, c, e, and f) were cyclised to *s*-triazolo[4,3-*a*]pyrimid-7-ones (XII) by reaction with lead tetra-acetate in benzene.[8]

However, when the benzylidene compound (XId) was treated in a similar way a mixture was obtained. The major component appeared to be the required *s*-triazolo-[4,3-*a*]pyrimid-7-one (u.v. spectrum) * but purification by recrystallisation or chromatography gave pure 4-benzyl-6-ethoxycarbonyl-2-phenyl-*s*-triazolo[1,5-*a*]-pyrimid-5-one (XIIIb), the minor component of the original mixture. Hydrolysis and decarboxylation of (XIIIb) gave 4-benzyl-2-phenyl-*s*-triazolo[1,5-*a*]pyrimid-5-one (XIIIa) which was also obtained by isomerisation of 8-benzyl-3-phenyl-*s*-triazolo[4,3-*a*]pyrimid-7-one (XIIc) in boiling aqueous piperidine.[14] In a similar way the product from the oxidation of the 2-benzylidene hydrazino-1-ethylpyrimid-6-one (XIb) was shown to be 6-ethoxycarbonyl-4-ethyl-2-phenyl-*s*-triazolo-[1,5-*a*]pyrimid-5-one (XIIId).

TABLE 2

The u.v. absorption spectra of 1-alkyl-2-benzylidene-hydrazinopyrimid-6-ones (XI) in ethanol

Substituents R^1	R^2	R^3	R^4	$\lambda_{max.}$ [mμ (log ε)]	
(XIa) Et	NHN=CHPh	H	H	230 (4·34)	320 (4·40)
(XIb) Et	NHN=CHPh	H	CO_2Et	232 (4·37)	320 (4·49)
(XIc) $PhCH_2$	NHN=CHPh	H	H	230 (4·36)	323 (4·41)
(XId) $PhCH_2$	NHN=CHPh	H	CO_2Et	233 (4·35)	320 (4·45)
(XIe) Me	NHN=CHPh	Me	H	230 (4·39)	320 (4·41)
(XIf) $PhCH_2$	NHN=CHPh	Me	H	230 (4·38)	315 (4·41)
					325 (4·42)

The ease of isomerisation of these 6-ethoxycarbonyl-*s*-triazolo[4,3-*a*]pyrimid-7-ones (XIIb and d) may be

* To be published.

[13] K. Shirakawa, *J. Pharm. Soc. Japan*, 1958, **78**, 1395 (*Chem. Abs.*, 1959, **53**, 8150).

[14] See K. Shirakawa, *J. Pharm. Soc. Japan*, 1960, **80**, 1550 (*Chem. Abs.*, 1961, **55**, 10, 450); Y. Makisumi and H. Kano, *Chem. Pharm. Bull.* (*Tokyo*), 1963, **11**, 67.

attributed to the increased susceptibility of the 5-position to nucleophilic attack by an electron donor (B) causing ring opening and rearrangement (see Scheme 3) (cf. the Dimroth rearrangement).[15]

The acid catalysed rearrangement of *s*-triazolo[4,3-*a*]-pyrimid-7-ones has not been reported previously, but the electrophilic character of the 5-position (see Scheme 4).

s-Triazolo[4,3-*a*]pyrimid-7-ones unsubstituted in the 3-position were best prepared by heating the benzylidene-hydrazino-compounds (XI) in formic acid containing dilute hydrochloric acid; in boiling acetic acid containing dilute hydrochloric acid (XIa), gave 8-ethyl-3-methyl-*s*-triazolo[4,3-*a*]pyrimid-7-one (XIIi).

TABLE 3

8-Substituted *s*-triazolo[4,3-*a*]pyrimid-7-ones (XII)

Substituents					Cryst. Solvent *	Yield (%)		Found (%)				Required (%)		
(XII;	R^1	R^2	R^3	R^4)			M. p.	C	H	N	Formula	C	H	N
(XIIa)	Ph	H	H	Et	E	31	210—212°	64·75	5·1	23·6	$C_{13}H_{12}N_4O$	65·0	5·05	23·3
(XIIb)	Ph	H	CO_2Et	Et										
(XIIc)	Ph	H	H	$PhCH_2$	C	78	191—193	71·3	4·65	18·35	$C_{18}H_{14}N_4O$	71·5	4·65	18·55
(XIId)	Ph	H	CO_2Et	$PhCH_2$										
(XIIe)	Ph	Me	H	Me	C	40	254—255	64·75	5·15	22·95	$C_{13}H_{12}N_4O$	65·0	5·0	23·3
(XIIf)	Ph	Me	H	$PhCH_2$	C	41	174—177	71·7	5·3		$C_{19}H_{16}N_4O$	72·15	5·1	
(XIIg)	H	H	H	$PhCH_2$	E	22		63·8	4·45		$C_{12}H_{10}N_4O$	63·7	4·45	
(XIIh)	H	H	H	Et	C	48		51·0	4·7	34·0	$C_6H_8N_4O$	51·2	4·9	34·15
(XIIi)	Me	H	H	Et		39·5		53·65	5·65	31·25	$C_8H_{10}N_4O$	53·95	5·65	31·25

* E = Ethanol, C = chloroform–light petroleum.

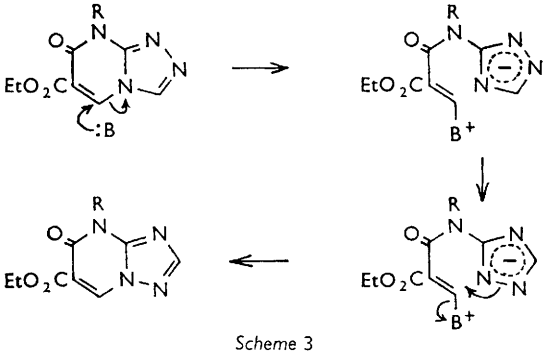
TABLE 4

4-Substituted *s*-triazolo[1,5-*a*]pyrimid-5-ones (XIII)

Substituents					Cryst. solvent *	Yield (%)		Found (%)				Required (%)		
(XIII;	R^1	R^2	R^3	R^4			M. p.	C	H	N	Formula	C	H	N
(XIIIa)	Ph	$PhCH_2$	H	H	I	45 †	182—184°	71·75	4·75	18·35	$C_{18}H_{14}N_4O$	71·5	4·65	18·55
(XIIIb)	Ph	$PhCH_2$	CO_2Et	H	E	67	164—166	67·5	5·05	14·95	$C_{21}H_{18}N_4O_3$	67·35	4·85	14·95
(XIIIc)	Ph	Et	H	H	E	50 †	206—209	64·75	5·2	23·6	$C_{13}H_{12}N_4O$	65·0	5·05	23·3
(XIIId)	Ph	Et	CO_2Et	H	E	44	142—143	61·7	5·1	18·0	$C_{16}H_{16}N_4O_3$	61·7	5·15	17·95

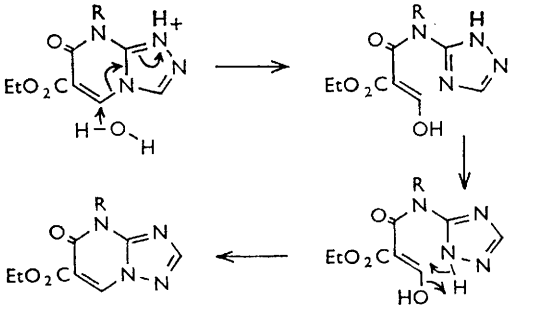
* E = Ethanol, I = isopropyl alcohol. † Hydrolysis of ester.

we found that the 6-ethoxycarbonyl derivatives (XIIb and d) rapidly give *s*-triazolo[1,5-*a*]pyrimid-5-ones



Scheme 3

(XIIIb and d) in boiling dilute acid. This again demonstrates the effect of the ethoxycarbonyl group increasing



Scheme 4

EXPERIMENTAL

All melting points are corrected. Light petroleum refers to the fraction b. p. 60—80°. T.l.c. was carried out on silica gel (H.F. 254) plates and spots located by viewing under a u.v. lamp. U.v. spectra were determined using a Beckman D.K. 2 spectrophotometer. I.r. spectra were determined using a Unicam SP 200 spectrophotometer.

The Reaction of Ethyl Imidates and 2-Hydrazinopyrimidines.—Typical examples are given below and the compounds listed in Table 1 were prepared in a similar manner.

5-Hydroxy-7-methyl-3-phenyl-s-triazolo[4,3-a]*pyrimidine* (IVb).[11]—(*a*) 2-Hydrazino-4-hydroxy-6-methylpyrimidine (2·8 g., 0·02 mole) was suspended in boiling ethanol (50 ml. and ethyl benzimidate hydrochloride (3·7 g., 0·02 mole) was added. The pyrimidine dissolved and the solution was heated under reflux for 5 hr., during which time solid began to separate. The solid was filtered off and crystallised from ethanol to give the product as needles (1·9 g., (46%), m. p. ≮300°, R_f 0·6 (Me_2CO).

The mother-liquors of the reaction mixture were concentrated and the residue diluted with water. The solid was collected and crystallised from ethanol to give 7-hydroxy-5-methyl-2-phenyl-*s*-triazolo[1,5-*a*]pyrimidine as a solid (0·2 g., 4%), m. p. ≮300°, R_f 0·8 (Me_2CO).

(*b*) 2-Hydrazino-4-hydroxy-6-methylpyrimidine (1·4 g., 0·01 mole) was dissolved in ethylene glycol (25 ml.) on the steam-bath and the solution treated with ethyl benzimidate

[15] D. J. Brown and J. S. Harper, *J. Chem. Soc.*, 1963, 1276.

hydrochloride (2·7 g., 0·015 mole). The solution was heated on the steam-bath for 4 hr. and then cooled. The crystalline solid was collected and recrystallised from ethanol to give the product as needles (1·35 g., 60%), m. p. $<300°$, R_f 0·6 (Me_2CO).

2-Ethoxycarbonylmethyl-s-triazolo[1,5-a]*pyrimidine* (Vg).—2-Hydrazinopyrimidine (11·0 g., 0·1 mole) in ethanol (250 ml.) was treated with ethyl ethoxycarbonylacetimidate hydrochloride [16] (20·0 g., 0·1 mole) and the solution was heated under reflux for 24 hr.

Ammonium chloride (3·2 g.) was removed by filtration and the filtrate evaporated. The residue was dissolved in chloroform, filtered, concentrated, and then diluted with ether. The resulting orange solid was collected and purified by chromatography on alumina with chloroform, followed by crystallisation from chloroform–light petroleum to give the *product* as plates (7·3 g.), m. p. 108—110°.

The reaction mixture mother-liquors were similarly chromatographed to give a further quantity of this product as pale yellow platelets (2·0 g.), m. p. 104—106°.

1-Benzyl-2-benzylidenehydrazino-5-ethoxycarbonylpyrimid-6-one (XId).—*N*-Benzyl-*N'*-benzylideneaminoguanidine (12·75 g., 0·05 mole) and ethyl β-ethoxy-α-ethoxycarbonylacrylate (25 ml., 0·06 mole) were heated together in boiling ethanol (50 ml.) under reflux for 18 hr. and then crystallised. The solid was collected, and recrystallised from n-butanol to give the *product* as pale yellow plates (10·7 g., 57%), m. p. 204—206° (Found: C, 67·05; H, 5·25; N, 14·8. $C_{21}H_{20}N_4O_3$ requires C, 67·0; H, 5·35; N, 14·9%).

1-Benzyl-2-benzylidenehydrazinopyrimid-6-one (XIc).—1-Benzyl-2-benzylidenehydrazino-5-ethoxycarbonylpyrimid-6-one (15·0 g., 0·04 mole) in boiling ethanol (1 l.) was treated with hot dilute sodium hydroxide solution (600 ml.). The solution was heated on the steam-bath and the ethanol distilled off under slightly reduced pressure. The aqueous residue was filtered and the filtrate acidified with hydrochloric acid. The solid was collected, washed with boiling water, and dried in a vacuum oven to give crude 1-benzyl-2-benzylidenehydrazino-6-oxo-5-pyrimidinecarboxylic acid as a solid (10·0 g.), m. p. 228—230° (decomp.).

This carboxylic acid was added to boiling quinoline (100 ml.) and the mixture heated under reflux for 2 hr. The solution was evaporated under reduced pressure and the residue dissolved in a small amount of ethanol and diluted with dilute hydrochloric acid. The solid was collected, washed with water, and recrystallised from aqueous ethanol (charcoal) to give the *product* as needles (5·0 g., 41%), m. p. 193—195° (Found: C, 71·3; H, 5·5; N, 18·3. $C_{18}H_{16}N_4O$ requires C, 71·0; H, 5·3; N, 18·4%).

2-Benzylidenehydrazino-5-ethoxycarbonyl-1-ethylpyrimid-6-one (XIb).—A solution of *S*-methylthiosemicarbazide hydriodide (116·5 g., 0·5 mole) in ethanol (250 ml.) was treated with ethylamine (90 ml., 30% ethanolic solution, 0·5 mole) and the mixture heated under reflux for 1 hr. The reaction mixture was concentrated and the crude *N*-amino-*N'*-ethylguanidine hydriodide [1] precipitated as a pale pink solid (54·0 g.), m. p. 60—65°, by the addition of ether. The crude aminoguanidine (0·235 mole) was dissolved in ethanol (200 ml.) with benzaldehyde (26·5 ml., 0·25 mole) and the mixture heated under reflux for 30 min. The solution was evaporated and the residue recrystallised twice from isopropyl alcohol to give *N*-benzylideneamino-*N'*-ethylguanidine hydriodide as a crystalline solid (58·7 g., 54%), m. p. 166—168° (Found: C, 37·55; H, 4·75; N, 71·5. $C_{10}H_{14}N_4$,HI requires C, 37·75; H, 4·75; N, 17·6%).

The hydriodide (10 g., 0·045 mole) suspended in water was basified with potassium hydroxide solution and extracted with chloroform. The chloroform extract was evaporated to give the guanidine-free base as a yellow syrup.

The syrup was dissolved in n-butanol (100 ml.) treated with ethyl β-ethoxy-α-ethoxycarbonylacrylate (10·5 g., 0·05 mole) and the solution heated under reflux for 18 hr. The solution was crystallised and the solid collected and recrystallised from n-butanol to give the *product* as pale yellow needles (6·8 g., 43%), m. p. 217—219° (Found: C, 61·30; H, 6·2; N, 17·8. $C_{16}H_{18}N_4O_3$ requires C, 61·15; H, 5·75; N, 17·85%).

2-Benzylidenehydrazino-1-ethylpyrimid-6-one (XIa).—2-Benzylidenehydrazino-5-ethoxycarbonyl-1-ethylpyrimid-6-one (25·0 g., 0·08 mole) in hot ethanol (1 l.) was treated with hot dilute sodium hydroxide solution (600 ml.) and the solution heated on the steam-bath, the ethanol distilling off under slightly reduced pressure for 1 hr.

The aqueous residue was filtered and the filtrate acidified with hydrochloric acid. The solid was collected, washed with boiling water, and crystallised from n-butanol to give 2-benzylidenehydrazino-1-ethyl-6-oxo-5-pyrimidinecarboxylic acid as a solid (19·5 g.), m. p. 233—236° (decomp.).

This carboxylic acid was added to boiling quinoline (150 ml.) and the solution heated under reflux for 2·5 hr. The solution was evaporated under reduced pressure and the residue treated with dilute hydrochloric acid. The solid was collected and recrystallised from ethanol (charcoal) to give the *product* as pale yellow needles (12·5 g., 68%), m. p. 212—214° (Found: C, 64·5; H, 5·95; N, 22·65. $C_{13}H_{14}N_4O$ requires C, 64·4; H, 5·8; N, 23·1%).

2-Benzylidenehydrazino-1,4-dimethylpyrimid-6-one (XIf).—2-Hydrazino-1,4-dimethylpyrimid-6-one [12] (0·23 g., 1·5 mmole) and benzaldehyde (0·5 ml., 5 mmole) were heated together in boiling ethanol (20 ml.) for 1 hr. under reflux. The mixture was diluted with water (30 ml.) and the solid collected and recrystallised twice from ethanol to give the *product* as needles (0·25 g., 69,%), m. p. 202—203° (Found: C, 64·45; H, 5·95; N, 23·0. $C_{13}H_{14}N_4O$ requires C, 64·6; H, 5·8; N, 23·1%).

1-Benzyl-2-benzylidenehydrazino-4-methylpyrimid-6-one (XIe).—(*a*) The title compound, m. p. 203—205°, was prepared in 5% yield by a literature [8] method (recorded m. p. 196—198°).

(*b*) *N*-Benzyl-*N'*-benzylideneaminoguanidine (3·2 g., 0·012 mole) and ethyl acetoacetate (2·0 g., 0·015 mole) were heated together on an oil-bath at 160—180° for 15 min. The hot reaction mixture was diluted with a small amount of ethanol and crystallised. The solid was collected and recrystallised twice from ethanol to give the *product* as plates (0·8 g., 21%), m. p. 196—199° [i.r. spectrum identical with sample from (*a*)].

8-Benzyl-s-triazolo[4,3-a]*pyrimid-7-one* (XIIg).—1-Benzyl-2-benzylidenehydrazinopyrimid-6-one (4·0 g., 0·013 mole) was heated under reflux in 10% hydrochloric acid (200 ml.) for 4 hr., the benzaldehyde distilling off.

The solution was filtered and the filtrate evaporated. The residue was dissolved in ethanol and concentrated; crude 1-benzyl-2-hydrazinopyrimid-6-one hydrochloride (1·25 g.), m. p. 205—208° (decomp.) precipitated on the addition of ether. The pyrimidone hydrochloride was dissolved in formic acid (10 ml.) containing sodium formate

[16] A. Pinner, *Ber.*, 1895, **28**, 478.

(0·35 g., 0·005 mole) and the solution heated on the steam-bath for 1·5 hr. The solution was evaporated, the residue washed with water and recrystallised twice from ethanol (charcoal) to give the *product* as needles (0·65 g., 22%), m. p. 194·5—196·5°, R_f 0·05 (EtOAc), 0·55 (Me_2CO).

8-*Ethyl*-s-*triazolo*[4,3-a]*pyrimid*-7-*one* (XIIh).—2-Benzylidenehydrazino-1-ethylpyrimid-6-one (2·0 g., 8 mmole) was heated under reflux in a mixture of formic acid (50 ml.), water (45 ml.), and hydrochloric acid (5 ml.) for 3 hr. The benzaldehyde together with some water was distilled off and the volume in the reaction flask maintained by slow addition of water. The reaction mixture was evaporated and the residue, neutralised with aqueous sodium hydrogen carbonate, was extracted with chloroform (9 × 50 ml.). The extract was concentrated and chromatographed on an alumina column with chloroform, the eluent evaporated, and the residue recrystallised from chloroform–light petroleum to give the *product* as needles (0·65 g., 48%), m. p. 164—166°, R_f 0·3 (Me_2CO).

8-*Ethyl*-3-*methyl*-s-*triazolo*[4,3-a]*pyrimid*-7-*one* (XIIi).—2-Benzylidenehydrazino-1-ethylpyrimid-7-one (2·0 g., 8 mmole) was heated under reflux in a mixture of acetic acid (25 ml.) and dilute hydrochloric acid (25 ml.) for 1·5 hr.

The benzaldehyde was distilled off and the solution evaporated. The residue was recrystallised from isopropyl alcohol (×2) to give the hydrochloride of the *product* as needles (0·4 g., 22%), m. p. 200—205°.

The mother-liquors were evaporated and the residue neutralised with aqueous sodium hydrogen carbonate. The solution was extracted with chloroform and the extract chromatographed on an alumina column with chloroform to give the *product* as buff needles (0·25 g., 17·5%), m. p. 170—172°, R_f 0·2 (Me_2CO).

The Reaction of Lead Tetra-acetate with 1-*Alkyl*-2-*benzylidenehydrazinopyrimid*-6-*ones*.—Typical examples are given below and the compounds in Tables 3 and 4 were similarly prepared.

8-*Benzyl*-3-*phenyl*-s-*triazolo*[4,3-a]*pyrimid*-7-*one* (XIIc).—1-Benzyl-2-benzylidenehydrazinopyrimid-6-one (0·45 g., 1·5 mmole) in warm benzene (30 ml.) was treated with lead tetra-acetate (0·75 g., 1·5 mmole). The solution was warmed on the steam-bath for 30 min. (lead acetate precipitated) and then treated with water (25 ml.). The mixture was filtered through filter aid and the organic layer separated from the filtrate. The benzene was evaporated under reduced pressure and the residue recrystallised from ethanol and then chloroform–light petroleum to give the *product* as needles (0·35 g., 78%), m. p. 191—193°, R_f 0·2 ($CHCl_3$), 0·9 (Me_2CO).

4-*Benzyl*-6-*ethoxycarbonyl*-2-*phenyl*-s-*triazolo*[1,5-a]-*pyrimid*-5-*one* (XIIIb).—1-Benzyl-2-benzylidenehydrazino-5-ethoxycarbonylpyrimid-6-one (1·8 g., 5 mmole) in methylene dichloride (50 ml.) was treated with lead tetra-acetate (2·4 g., 5 mmole) in methylene dichloride (50 ml.) and the mixture left at room temperature for 1 hr.

The reaction mixture was treated with water, filtered through filter aid, and the organic layer evaporated under reduced pressure. The residue was diluted with ether and crystallised to give crude 8-benzyl-6-ethoxycarbonyl-3-phenyl-*s*-triazolo[4,3-*a*]pyrimid-7-one (XIId) as needles (1·3 g.), m. p. 165—168°, R_f 0·25 ($CHCl_3$) and a minor component R_f 0·30 ($\lambda_{max.}$ 250 mμ). Repeated recrystallisation of this *s*-triazolo[4,3-*a*]pyrimid-7-one from ethanol or chromatography on silica with chloroform gave the *s*-triazolo[1,5-*a*]pyrimid-5-one as needles, m. p. 164—166°, R_f 0·3 ($CHCl_3$), mixed m. p. 135—137° with crude *product*.

Isomerisation of 6-*Ethoxycarbonyl*-s-*triazolo*[4,3-a]*pyrimid*-7-*ones* (XIIb *and* XIId).—8-Benzyl-6-ethoxycarbonyl-3-phenyl-*s*-triazolo[4,3-*a*]pyrimid-7-one (XIId) (0·6 g., 2·5 mmole) was heated in boiling ethanol (40 ml.) containing dilute hydrochloric acid (10 ml.) for 10 min. under reflux. The solution was crystallised and the solid collected to give 4-benzyl-6-ethoxycarbonyl-2-phenyl-*s*-triazolo[1,5-*a*]-pyrimid-5-one (XIIIb) as needles (0·5 g., 83%), m. p. 164—166°, R_f 0·30 ($CHCl_3$).

8-Ethyl-6-ethoxycarbonyl-3-phenyl-*s*-triazolo[4,3-*a*]-pyrimid-7-one (XIIb) (0·6 g., 2·5 mmole) [m. p. 130—132°, R_f 0·10, trace 0·25 ($CHCl_3$)] was suspended in boiling dilute hydrochloric acid (75 ml.) under reflux. The ester dissolved and a solid immediately separated. The mixture was cooled and the solid collected to give 6-ethoxycarbonyl-4-ethyl-2-phenyl-*s*-triazolo[1,5-*a*]pyrimid-5-one (XIIId) as needles (0·6 g., 100%), m. p. 136—139°, R_f 0·25 ($CHCl_3$), mixed m. p. 115° with starting material.

4-*Benzyl*-2-*phenyl*-s-*triazolo*[1,5-a]*pyrimid*-5-*one* (XIIIa).—(*a*) 4-Benzyl-6-ethoxycarbonyl-2-phenyl-*s*-triazolo[1,5-*a*]-pyrimid-5-one (3·0 g., 8 mmole) in acetic acid (150 ml.) and dilute hydrochloric acid (50 ml.) was heated under reflux for 2 hr. and the solution crystallised. The solid was collected and recrystallised from dilute acetic acid to give 4-benzyl-5-oxo-2-phenyl-*s*-triazolo[1,5-*a*]pyrimidine-6-carboxylic acid as needles (2·5 g.), m. p. 253—254°. This carboxylic acid was added to boiling quinoline (50 ml.) and the solution heated under reflux for 2 hr. The solution was evaporated and the residue triturated with dilute hydrochloric acid, washed with water, and recrystallised twice from isopropyl alcohol to give the *product* as needles (1·3 g., 45%), m. p. 182—184°.

(*b*) 8-Benzyl-3-phenyl-*s*-triazolo[4,3-*a*]pyrimid-7-one (0·2 g.) was heated under reflux in a mixture of piperidine (6 ml.) and water (2 ml.) for 1 hr. The solution was evaporated and the residue diluted with dilute hydrochloric acid. The solid was collected and recrystallised from ethanol to give the product as buff needles (0·045 g.), m. p. 174—177° [i.r. spectrum identical with spectrum of sample from (*a*)].

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