610. s-*Triazolopyrimidines. Part II.*[1] *Synthesis as Potential Therapeutic Agents*

By G. W. Miller and F. L. Rose

3-Amino-*s*-triazolo[4,3-*c*]pyrimidines and the isomeric 2-amino-*s*-triazolo-[2,3-*c*]pyrimidines, of the type described in Part I,[1] together with a number of α-substituted amino-derivatives, have been prepared, either directly or indirectly, from the corresponding 4-thioureido-, 4-semicarbazido-, and 4-thiosemicarbazido-pyrimidines. The circumstances under which compounds of the [4,3-*c*] series isomerise into those of the [2,3-*c*] series are discussed.

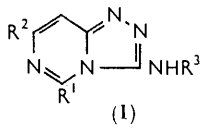
In Part I [1] is described the synthesis of a number of 3-amino-*s*-triazolo[4,3-*c*]pyrimidines (I; $R^3 = H$) by the interaction of cyanogen chloride with the hydrazinopyrimidines (II), and the preparation is discussed of the isomeric 2-amino-*s*-triazolo[2,3-*c*]pyrimidines (III; $R^3 = H$), either by isomerisation of (I; $R^3 = H$), for example in the presence of dilute hydrochloric acid, or directly, by conducting the reaction with cyanogen chloride in hydrochloric acid solution. The substances listed all carried one or more hydrocarbon substituents in the pyrimidine nucleus and were notable biologically, especially the compound (III; $R^1 = Pr^n$; $R^2 = Me$, $R^3 = H$), for the protection they afforded guinea-pigs against the toxic effects of inhaled histamine spray. This investigation has been extended to include the preparation of substances carrying substituents in the primary amino-groups, and which clearly could not be obtained by the routes already described. The substituted amino-compounds obtained by these later methods were regarded as *s*-triazolo[2,3-*c*]-pyrimidines, mainly on the basis of their closely similar spectroscopic behaviour, particularly in the ultraviolet region, to the parent primary amines. At the same time, the new synthetic routes have been applied to the preparation of the latter, and have provided additional circumstantial evidence for the structures already adduced for these compounds.[1] Another aspect of the research has been concerned with the preparation of triazolopyrimidines (XIV) and (XV), having oxo-groups in the triazole ring, and also the bromo-derivative (XIX). These were considered to be of potential biological interest in their own right. The bromo-derivative (XIX) was also of value as an intermediate for the preparation of the corresponding amines. The ethoxytriazolopyrimidine (XX) was also prepared from it.

2-*Substituted Amino*-s-*triazolo*[2,3-c]*pyrimidines.*—The following several methods of preparation have been investigated. Some were fairly general, whilst others were limited.

(a) *From semicarbazides.* Largely because of the subsequent behaviour of the compound, it was assumed that the product resulting from the reaction of cyanic acid with the hydrazine (II; $R^1 = Pr^n$, $R^2 = Me$) was the semicarbazide (IV) rather than one of the isomers which would derive from the alternative attachment of the carbamoyl residue to one or other of the remaining nitrogen atoms. Ring-closure was effected in the first experiments by the action of phosphoryl chloride, but gave not the expected 3-amino-*s*-triazolo[4,3-*c*]pyrimidine, but the [2,3-*c*]-isomer (III; $R^1 = Pr^n$, $R^2 = Me$, $R^3 = H$).

[1] Part I, G. W. Miller and F. L. Rose, *J.*, 1963, 5642.

It seems most likely that formation of the latter proceeded through the initial production of the former, with subsequent isomerisation, either as a result of the heat applied, or by the influence of the hydrochloric acid produced during the reaction. In any event, the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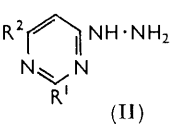
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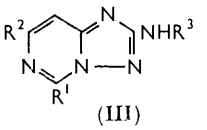
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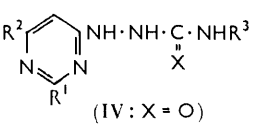
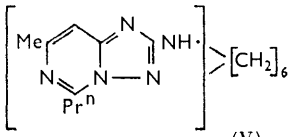

(IV: X = O)
(VI: X = S)
(XIII: X = N·NH$_2$)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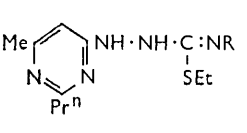
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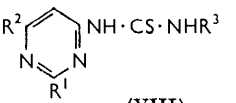
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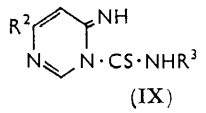
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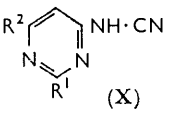
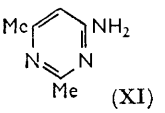
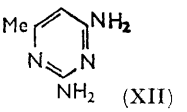

(X)


(XI)


(XII)

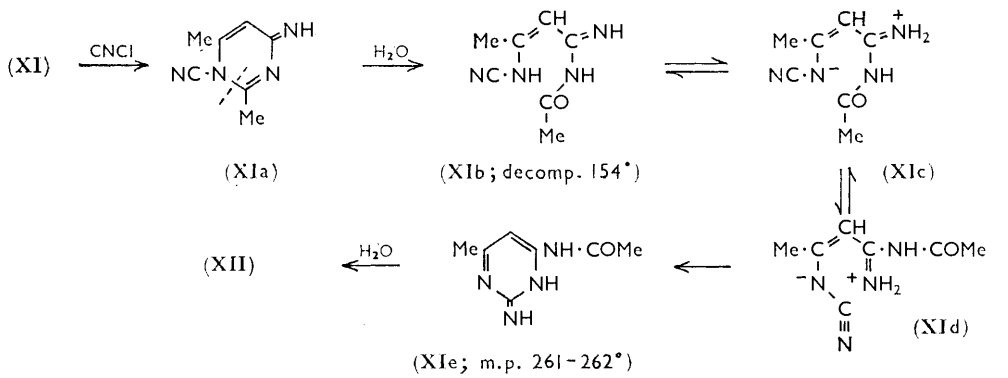
yield was small. The use of methyl isocyanate gave a similar result, the substance formed being identical with (and thus confirming the structure of) the product described in Part I, which was obtained by methylation of the acetyl derivative (III; $R^1 = Pr^n$, $R^2 = Me$, $R^3 = Ac$) in an alkaline medium. As the Experimental section shows, the reaction was applicable generally to semicarbazidopyrimidines carrying inert substituents, even to more complex derivatives leading, for example, to the product of probable structure (V). An anomaly was provided by (IV; $R^1 = Pr^n$, $R^2 = Me$, $R^3 = PhCH_2{\cdot}CH_2$) that gave, in addition to the expected triazolopyrimidine (III), a by-product having the same empirical formula as the starting material, but which only absorbed weakly in the ultraviolet region. The t-octyl derivative (IV; $R^1 = Pr^n$, $R^2 = Me$, $R^3 = Oc^t$) gave a by-product identified as (III; $R^1 = Pr^n$, $R^2 = Me$, $R^3 = H$) formed, presumably, through elimination of *t*-octylamine instead of water. Other methods for the dehydration of the semicarbazides (IV) were examined on a limited scale. Thus (IV; $R^1 = Pr^n$, $R^2 = Me$, $R^3 = Bu^n$) heated with phosphoric oxide in xylene gave a small yield of the corresponding *s*-triazolo-[2,3-*c*]pyrimidine, but no such product arose from an attempted dehydration with thionyl chloride. Simple fusion by heat was unsuccessful, while prolonged refluxing in *o*-dichlorobenzene gave the hydroxytriazolopyrimidine (XIV) (see below), with *NN'*-di-*n*-butylurea as a by-product.

(b) *From thiosemicarbazides.* The required parent thiosemicarbazide (VI; $R^1 = Pr^n$, $R^2 = Me$, $R^3 = H$) and its methyl homologue ($R^3 = Me$) were both readily prepared by reaction of (II; $R^1 = Pr^n$, $R^2 = Me$, $R^3 = H$) in 2-ethoxyethanol with ammonium thiocyanate or methyl isothiocyanate, respectively, and were desulphurised without isolation by heating with litharge. The products were difficult to isolate and purify, but they were shown conclusively to contain 2-amino- and 2-methylamino-*s*-triazolo[2,3-*c*]pyrimidines, respectively. On the assumption that the 4,3-*c* isomers were first produced in the desulphurisation reaction, then rearrangement could probably be attributed to the high temperature employed. A variation of this route gave (III; $R^1 = Pr^n$, $R^2 = Me$, $R^3 = H$) and (III; $R^1 = Pr^n$, $R^2 = Me$, $R^3 = Bu^i$) from the corresponding *S*-alkyl intermediates (VII; R = H or Bu^i), prepared by the action of ethyl iodide on the thiosemicarbazides. In the latter case, cyclisation was shown to occur simply by heating the thiouronium salt alone in boiling 2-ethoxyethanol, and without the use of litharge.

(c) *From the corresponding bromo-compound.* Several mono- and di-substituted amino-*s*-triazolo[2,3-*c*]pyrimidines were prepared from the bromo-derivative (XIX) and the

appropriate amine, in a suitable solvent at an elevated temperature. With ammonia, compound (XIX) yielded the corresponding amine (III; $R^1 = Pr^n$, $R^2 = Me$, $R^3 = H$). The usefulness of this reaction was limited chiefly by the difficulty of obtaining the bromo-intermediate, referred to below. The preparation of other substituted amino-*s*-triazolo-[2,3-*c*]pyrimidines by a related reaction from the corresponding alkyl sulphones will be dealt with in the following Paper.

(d) *From thioureas.* *s*-Triazolo[2,3-*c*]pyrimidines were obtained by methods which did not need to presuppose the initial formation of the [4,3-*c*]-isomers, starting from the thioureidiopyrimidines (VIII). Several routes to these intermediates were explored. Thus, substances having the correct empirical formula resulted from the action of alkyl isothiocyanates on the corresponding 6-aminopyrimidines. They were presumed to have the formulation (VIII), rather than (IX), or the further alternative structure having the thiocarbamoyl residue attached to the other ring nitrogen. The last two possibilities would not permit ultimate cyclisation to a triazolopyrimidine. An attempt was made to prepare the thiourea (VIII; $R^1 = R^2 = R^3 = Me$) by an unambiguous route in which 6-chloro-2,4-dimethylpyrimidine was heated with potassium thiocyanate, according to the method of Wheeler and Bristol.[2] Treatment of the crude reaction product with monomethylamine gave a substance $C_6H_8N_2S$, thought to be 2,4-dimethyl-6-mercaptopyrimidine, from which it was inferred that the attachment of the thiocyanato-residue to the pyrimidine nucleus, to the extent that it had occurred, was through a sulphur rather than a nitrogen atom. A less direct, but seemingly more feasible, route was then explored which required first the synthesis of the 6-cyanamidopyrimidines (X). To this end, the availability of cyanogen chloride prompted an attempt to introduce the cyano-group directly into the side-chain amino-group of 6-amino-2,4-dimethylpyrimidine (XI). The result was most unexpected. No uptake of cyanogen chloride by the amine was observed in dilute aqueous hydrochloric acid solution, but absorption occurred in the presence of sodium hydroxide. The only product, isolated after considerable manipulation, was a base that analysed for $C_5H_5N_4$ and was identified as 2,6-diamino-4-methylpyrimidine (XII), suggesting the apparent but unlikely replacement of a methyl group by an amino-group. The reaction was then investigated under milder conditions. In the presence of aqueous sodium hydrogen carbonate, cyanogen chloride was taken up by the aminopyrimidine (XI) to give a substance $C_7H_{10}N_4O$ which changed its physical form on heating to 154° but did not lose the elements of water when dried at 100° *in vacuo*. It was soluble in cold dilute sodium hydroxide. A solution in water held at the boil for a few minutes deposited, on cooling, a crystalline solid, m. p. 261—262°, that also analysed as $C_7H_{10}NO_4$. Both of these compounds when kept in cold dilute sodium hydroxide, or more rapidly when warmed, were converted into the diamine (XII). The following scheme was suggested for a probable course of this series of reactions:



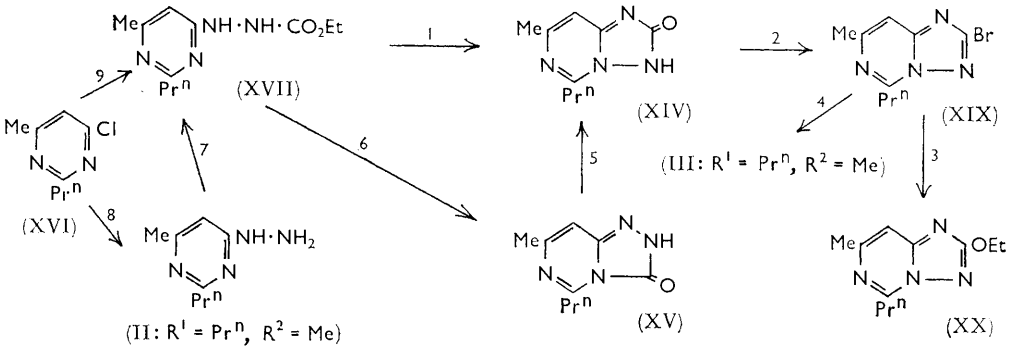
[2] H. L. Wheeler and H. S. Bristol, *Amer. Chem. J.*, 1905, **33**, 448.

It would be expected that the intermediate (XIa; not isolated) would be unstable in the presence of aqueous alkali, and that it would decompose rapidly to the amide (XIb). A strong band at 2170 cm.$^{-1}$ in the infrared absorption spectrum of the latter provided good evidence in support of a cyanamide configuration, while a band at 1710 cm.$^{-1}$ present in the solid, and which persisted in a dimethyl sulphoxide solution, was attributed to the carbonyl group. The solubility of (XIb) in aqueous caustic alkali also accorded with the structure suggested. In aqueous media, the ionisation shown for (XIc) would be expected and would probably promote the re-orientation to (XId), and thence on heating to the pyrimidine (XIe). A strong band at 1700 cm.$^{-1}$ in dimethyl sulphoxide solution (due to the acetamido-group, and absent from XII) supported the structure indicated, as did the emergence of basic properties. The overall result could equally well be explained by assuming attachment of the cyano-group to the other ring-nitrogen, followed by an analogous sequence of reactions. A further alternative scheme could be postulated in which the initial attachment of the cyano-group was to the side-chain amino-group (X), but this course was considered unlikely in view of the comparative stability of 2-cyanamidopyrimidines [3] and of the closely related compound (X; $R^1 = Pr^n$, $R^2 = Me$), which was ultimately prepared by the action of sodium cyanamide on 6-chloro-4-methyl-2-*n*-propylpyrimidine in alcohol. The latter compound with aqueous ammonium sulphide yielded the thioureidopyrimidine (VIII; $R^1 = Pr^n$, $R^2 = Me$, $R^3 = H$) and the close resemblance of the absorption spectra obtained with this substance to those from compounds prepared by the thiocyanate routes as described above, provided circumstantial proof of its structure. The thioureidopyrimidines were converted into the corresponding triazolopyrimidines by treatment with hydrazine hydrate in boiling 2-ethoxyethanol, in the presence of litharge. Reconversion into the cyanamidopyrimidines might have been an intermediate stage in the course of this reaction, but in any event it must be assumed that the aminoguanidines (XIII) were also formed as intermediates from which the triazolopyrimidines (III) were then formed by the elimination of ammonia. The triazolopyrimidines successfully prepared in this manner included (III; $R^1 = R^2 = Me$, $R^3 = H$), and related highly alkylated examples such as 8-ethyl-2-methylamino-5,7-di-*n*-propyl-*s*-triazolo[2,3-*c*]pyrimidine. (The aminopyrimidine required for the latter was " kyanpropin," the self-condensation product of butyronitrile, obtained in good yield after considerable work on the reaction, by the action of a large excess of sodium methoxide under heat and pressure.) A method which was possibly related to this process, in that it may involve an aminoguanidinopyrimidine intermediate, was the preparation of compound (III; $R^1 = Pr^n$, $R^2 = Me$, $R^3 = H$) from the hydrazinopyrimidine (II; $R^1 = Pr^n$, $R^2 = Me$, $R^3 = H$), and the *S*-ethylthiouronium or guanidinium salt. An attempt to prepare a triazolopyrimidine directly from the reaction of 6-chloropyrimidine with aminoguanidine hydrogen carbonate was unsuccessful, and likewise failure attended the attempted condensation of (X; $R^1 = Pr^n$, $R^2 = Me$) with hydroxylamine hydrochloride to give the *N*-hydroxyguanidinopyrimidine, which would be expected to yield the triazolopyrimidine by dehydration. The 6-ureidopyrimidine was isolated instead.

Hydroxytriazolopyrimidines.—Most of the preparations of this type have been based on the structurally favoured 6-chloro-4-methyl-2-*n*-propylpyrimidine (XVI), and the related hydrazinopyrimidine (II; $R^1 = Pr^n$, $R^2 = Me$, $R^3 = H$). The former compound and ethoxycarbonylhydrazine, or the latter compound and ethyl chloroformate, gave a product assumed to have the structure (XVII). The monohydrate of this substance, on fusion, gave a small yield of a compound whose ultraviolet absorption spectrum, particularly when measured in the presence of alkali, was similar to that of the triazolopyrimidine (III; $R^1 = Pr^n$, $R^2 = Me$, $R^3 = H$), and whose infrared spectrum was consistent with the presence of the lactam group. The keto structure (XIV) was therefore assigned to the compound, rather than the tautometric hydroxytriazole configuration. The action of phosphorus tribromide or phosphoryl bromide gave the bromo-compound (XIX), having

[3] S. Birtwell, *J.*, 1953, 1725.

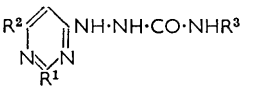
similar ultraviolet absorption characteristics to the parent lactam, and to the corresponding aminotriazolopyrimidine into which it was converted by the action of ammonia. The aminotriazolopyrimidine could also be reconverted into compound (XIX), but in small yield, by the action of bromine and sodium nitrite in aqueous hydrobromic acid. When the carbamate (XVII) was heated in boiling dry *o*-dichlorobenzene solution rather than to fusion, the elements of ethanol were lost, but a different principal product was obtained, to which the isomeric structure (XV) was assigned. Infrared data again agreed with the lactam structure rather than that of the tautomeric hydroxy-compound, while the ultraviolet absorption was characteristic of the related amino-*s*-triazolo[4,3-*c*]pyrimidines. An attempt to prepare the corresponding 3-bromo-derivative, isomeric with (XIX), was unsuccessful. The retention of the 4,3-*c* configuration even when ring-closure was effected in *o*-dichlorobenzene under reflux was surprising in view of the normal sensitivity to heat of the 3-amino-*s*-triazolo[4,3-*c*]pyrimidines. Equally surprising was the observation that the carbamate (XVII) under reflux in phosphoryl chloride gave the 4,3-*c* compound (XV), although the yield was poor. The same substance was also obtained when a solution of the hydrazine (II; $R^1 = Pr^n$, $R^2 = Me$, $R^3 = H$) in dry toluene was treated at room temperature with a solution of phosgene in the same solvent. When this reaction was



1, Fusion; 2, $POBr_3$; 3, NaOEt; 4, NH_2R^3; 5, NaOH; 6, heat in *o*-dichlorobenzene or $POCl_3$; 7, $ClCO_2Et$; 8, N_2H_4; 9, $NH_2{\cdot}NH{\cdot}CO_2Et$

carried out under aqueous conditions, either in the presence of dilute hydrochloric acid or a sodium acetate–acetic acid buffer, a somewhat unstable compound was formed of empirical formula $C_9H_{14}N_4O_2$, sparingly soluble in water, but readily soluble in dilute sodium carbonate. The structure of this compound has not been further investigated, but on treatment with aqueous sodium hydroxide it was converted into the lactam (XIV). As has already been mentioned, the triazolopyrimidine (XIV) was also obtained by heating the semicarbazide (IV; $R^1 = Pr^n$, $R^2 = Me$, $R^3 = Bu^n$) in *o*-dichlorobenzene. The same semicarbazide with phosphoryl chloride gave the corresponding *n*-butylamino-*s*-triazolo-[2,3-*c*]pyrimidine (III; $R^1 = Pr^n$, $R^2 = Me$, $R^3 = Bu^n$). The conditions for the conversion of the triazolo[4,3-*c*]pyrimidine (XV) into the [2,3-*c*]-isomer (XIV) was next investigated. The former was recovered largely unchanged when dissolved in cold dilute sodium hydroxide and re-precipitated immediately with acid, but in cold N-sodium hydroxide overnight, isomerisation was complete. No isomerisation was detected after short contact with N-hydrochloric acid at room temperature, while on long standing decomposition took place and was accompanied by the smell of butyric acid, evidently formed from breakdown of the pyrimidine ring. The stability of the [4,3-*c*]-isomer to boiling *o*-dichlorobenzene has already been mentioned, but the addition of formic acid brought about isomerisation. No hydroxytriazolopyrimidine of either series was obtained from the action of urea, *N*-methylurea, diethyl carbonate, or di-*n*-butyl carbonate, on the parent hydrazinopyrimidine (II; $R^1 = Pr^n$, $R^2 = Me$, $R^3 = H$). Finally the bromo-compound

TABLE 1

6-Semicarbazidopyrimidines 

R¹	R²	R³	Crude yield (%)	Found (%) C	H	N	Formula	Required (%) C	H	N	M. p., etc.
Pr^n	Me	Et	83	55·2	8·0	29·0	$C_{11}H_{19}N_5O$	55·7	8·1	29·5	Prisms,[1] 209—210°
,,	,,	CH_2·CH=CH_2	68	57·6	7·7	27·9	$C_{12}H_{19}N_5O$	57·8	7·7	28·1	200° [2]
,,	,,	Bu^n	80	58·5	8·5	26·3	$C_{13}H_{23}N_5O$	58·8	8·7	26·4	Plates,[1] 186—188°
,,	,,	CH_2CO_2Me	87	51·7	7·0	24·6	$C_{12}H_{19}N_5O_3$	51·2	6·8	24·9	164°
,,	n-C_7H_{15}	Bu^n	95	65·3	10·1	20·1	$C_{19}H_{35}N_5O$	65·3	10·1	20·0	174—176°
n-C_5H_{11}	Me	CH_2·CH=CH_2	77	59·6	8·4	25·2	$C_{14}H_{23}N_5O$	60·6	8·4	25·2	180—182° [3]
Pr^n	CF_3	Bu^n	79	48·5	6·4	22·0	$C_{13}H_{20}F_3N_5O$	48·9	6·3	21·1	Needles,[4] 177—178°
,,	Me	CH_2·CH_2Ph	84	65·3	7·6	22·4	$C_{17}H_{23}N_5O$	65·1	7·4	22·4	204°
,,	Pr^n	Me	94	57·5	8·7	28·2	$C_{12}H_{21}N_5O$	57·3	8·4	27·4	184° [1]
,,	Me	Ph	100	63·0	6·6	24·8	$C_{15}H_{19}N_5O$	63·1	6·7	24·6	208—209° [1]
,,	,,	$[CH_2]_6$<	72	56·9	8·1	28·8	$C_{24}H_{40}O_2N_{10}$	57·6	8·0	28·0	224—225° [1]

[1] From ethanol. [2] From ethanol–ethyl acetate. [3] From ethyl acetate. [4] From ether.

TABLE 2

Aminotriazolopyrimidines (III; R¹ = Pr^n, R² = Me)

R³	Found (%) C	H	N	Formula	Required (%) C	H	N	M. p., etc.	$\lambda_{max.}$ (mμ) (ε)
NH_2	—	—	—	—	—	—	—	Plates,[1] 168—170°	—
Pr^{i}NH	61·8	8·3	—	$C_{12}H_9N_5$	61·8	8·2	—	94—95°	233(42,300), 301(2500)
HO·C_2H_4 ...	57·4	7·4	29·3	$C_{11}H_{17}N_5O$	56·2	7·3	29·8	Needles,[3] 129—130°	232(46,100), 295(2500)
n-Hexyl–NH	65·2	9·1	25·3	$C_{15}H_{25}N_5$	65·4	9·2	25·4	Plates,[2] 73—74°	233(41,200), 301(2600)
Benzyl–NH	68·6	6·8	24·4	$C_{16}H_{19}N_5$	68·3	6·8	24·9	Plates,[2] 112—114°	213(12,500), 234(46,400), 298(2600)
$(HO·C_2H_4)_2N$	55·7	7·6	24·6	$C_{13}H_{21}N_5O_2$	55·9	7·6	25·0	Needles,[3] 97—98°	239(36,100), 307(2600)
Piperidino ...	64·7	8·0	27·0	$C_{13}H_{21}N_5$	64·8	8·2	27·0	Needles,[2] 80—82°	237(39,500), 307(3100)
Morpholino	59·3	7·3	26·3	$C_{13}H_{19}N_5O$	59·75	7·3	26·8	92—94°	—

[1] From ethyl acetate. Identical with authentic material (Part I). [2] From light petroleum (b. p. 60—80°). [3] From ethyl acetate.

(XIX), on treatment with sodium ethoxide, gave the corresponding ethoxy-derivative (XX), whose ultraviolet absorption spectrum very closely resembled that of the corresponding 2-aminotriazolopyrimidine (III; R¹ = Pr^n, R² = Me, R³ = H).

EXPERIMENTAL

Analytical samples were usually dried *in vacuo* over phosphoric oxide at room temperature if m. p. <100°, at *ca.* 60° if m. p. 100—150°, and at *ca.* 100° if m. p >150°. Nitrogen values were determined by using extra oxygen.

Ultraviolet spectra were determined for solutions in redistilled methanol, using an Optica CF4 DR spectrophotometer.

Infrared spectra were measured with a Perkin–Elmer model 21 and KBr discs or Nujol mulls.

4-Methyl-2-n-propyl-6-semicarbazidopyrimidine.—Sodium cyanate (1 g.) was added to a solution of 6-hydrazino-4-methyl-2-n-propylpyrimidine (2·5 g.) in hydrochloric acid (15 ml., N). The mixture was heated on a steam-bath for 30 min., then cooled to 0°. The precipitate was filtered off, washed first with ice-cold water, then with ice-cold ethanol, and dried, to yield the *semicarbazidopyrimidine* (2·75 g.), as an amorphous pale yellow solid, m. p. 239—240° (Found: C, 51·3; H, 7·4; N, 32·8. $C_9H_{15}N_5O$ requires C, 51·65; H, 7·2; N, 33·5%).

2,4-Dimethyl-6-(4′-methylsemicarbazido)pyrimidine.—A solution of methyl isocyanate (5 g.) in dry dioxan (25 ml.) was added gradually to a solution of 6-hydrazino-2,4-dimethylpyrimidine (10 g.) in boiling dry benzene (125 ml.). The suspension formed was boiled under reflux for

10 min., cooled to room temperature, diluted with ether, and cooled. The residual colourless solid, 13 g., m. p. 232°, was filtered off, washed with ether, and dried. A small portion was crystallised from 2-ethoxyethanol to give the *semicarbazidopyrimidine* as a colourless solid, m. p. 234° (Found: C, 49·0; H, 6·6. $C_8H_{13}N_5O$ requires C, 49·2; H, 6·7%).

4-*Methyl*-6-(4′-*methylsemicarbazido*)-2-*n*-*propylpyrimidine*.—6-Hydrazino-4-methyl-2-n-propylpyrimidine (2 g.) was dissolved in boiling dry benzene (25 ml.). To the hot solution there was gradually added a solution of methyl isocyanate (0·6 g.) in dry benzene (75 ml.). The suspension obtained was heated under reflux for 7 min. then cooled to room temperature. Addition of an equal volume of ether, followed by filtration, gave a colourless solid (2·2 g., m. p. 222—224°). The *product* crystallised from ethanol as colourless needles, m. p. 225—226° (Found: C, 53·8; H, 7·6; N, 31·3. $C_{10}H_{17}N_5O$ requires C, 53·8; H, 7·7; N, 31·4%).

4-*Methyl*-2-*n*-*propyl*-6-(4′-*t*-*octylsemicarbazido*)*pyrimidine*.—A solution of t-octyl isocyanate (5 g.), in dry benzene (15 ml.), was added gradually to a solution of 6-hydrazino-4-methyl-2-n-propylpyrimidine (5 g.), in dry benzene (15 ml.). The mixture was boiled under reflux for 2 hr., and evaporated to dryness under reduced pressure. The residue was dissolved in ether (20 ml.) to yield the crude *semicarbazidopyrimidine* (5·3 g., m. p. 139—140°), which gave colourless microcrystals from ether, m. p. 140° (Found: C, 62·6; H, 9·7; N, 21·6. $C_{17}H_{31}N_5O$ requires C, 63·5; H, 9·2; N, 21·8%).

The *semicarbazidopyrimidines* listed in Table 1 were prepared by methods similar to the above, and crystallised from either ethyl acetate or ethanol.

Hydroxytriazolopyrimidines.—3-*Hydroxy*-7-*methyl*-5-*n*-*propyl*-s-*triazolo*[4,3-c]*pyrimidine*. A solution of 6-chloro-4-methyl-2-n-propylpyrimidine (8·1 g.), in ethanol (50 ml.), was added dropwise to a solution of ethoxycarbonylhydrazine (10 g.), in boiling ethanol (50 ml.). The mixture was boiled under reflux for 16 hr., then evaporated to dryness under reduced pressure. Addition of sodium acetate to a solution of the residue in water (100 ml.) gave 6-(2′-*ethoxycarbonylhydrazino*)-4-*methyl*-2-*n*-*propylpyrimidine* as a colourless solid (11 g., m. p. 98—100°). Crystallisation of a portion of this material from ethyl acetate, followed by prolonged drying at 60° *in vacuo*, yielded colourless needles, m. p. 112—114° (Found: C, 55·5; H, 7·8; N, 23·7. $C_{11}H_{18}N_4O_2$ requires C, 55·4; H, 7·6; N, 23·5%), $\lambda_{max.}$ 206, 233, and 266 mμ (ε 9000, 10,700, and 6100). When the product was air-dried, it had m. p. 100—103° (Found: C, 51·7; H, 7·7. $C_{11}H_{18}N_4O_2,H_2O$ requires C, 51·6; H, 7·9%). The same substance (m. p., infrared and ultraviolet spectra) was formed when a solution of ethyl chloroformate (1·2 g.), in dry ethyl acetate (5 ml.), was added with cooling to a solution of the hydrazinopyrimidine (1·7 g.) in dry ethyl acetate (20 ml.), by collecting the white solid which separated, dissolving it in water (10 ml.), adding sodium acetate, and crystallising the precipitate from ethyl acetate.

The anhydrous ethoxycarbonyl derivative (10 g.) and phosphoryl chloride (25 ml.) were boiled under reflux for 3·5 hr., and the mixture concentrated under reduced pressure, cooled, poured on ice and water, and adding sodium hydrogen carbonate to neutralise acidity. Extraction with ethyl acetate yielded a colourless solid (1·3 g.), which gave the *triazolo*[4,3-c]-*pyrimidine* as colourless needles (0·5 g., m. p. 132—134°) from alcohol (Found: C, 56·4; H, 6·3; N, 28·8. $C_9H_{12}N_4O$ requires C, 56·2; H, 6·3; N, 29·1%), $\lambda_{max.}$ 207, 247, and 317 mμ (ε 10,000, 10,400, and 6300), $\nu_{max.}$ 1708 (KBr), 1720 (CCl_4), and 3150 cm.$^{-1}$. The same product (4·6 g.) but containing traces of the isomeric triazolo[2,3-*c*]pyrimidine, was obtained when the ethoxycarbonyl derivative (10 g.) was boiled under reflux with *o*-dichlorobenzene (50 ml.) for 40 hr., and the residue left after evaporation of the solvent was recrystallised from ethanol and finally ethyl acetate. In another route, a solution of 6-hydrazino-4-methyl-2-n-propylpyrimidine (6 g.) in dry toluene (30 ml.) was added to a well-stirred solution of phosgene (6·5 g.) in dry toluene (50 ml.), below 25°. The resulting suspension was cooled in ice–water. The solid (9 g.) was filtered off, washed first with dry toluene and then with light petroleum (b. p. 40—60°), and dissolved in water (50 ml.). Addition of sodium acetate gave the triazolo[4,3-*c*]-pyrimidine (3·4 g.), which crystallised from ethyl acetate as colourless needles (2·05 g., m. p. 132°).

2-*Hydroxy*-7-*methyl*-5-n-*propyl*-s-*triazolo*[2,3-*c*]*pyrimidine*. The above 6-(2′-ethoxycarbonylhydrazino)-4-methyl-2-n-propylpyrimidine hydrate (2 g.) was heated for 4 hr. in an open tube at an oil-bath temperature of 200°. The cooled dark coloured melt crystallised from ethanol (charcoal) to yield the *triazolopyrimidine* as colourless needles (0·25 g., m. p. 186—188°) (Found: C, 56·6; H, 6·3; N, 29·0. $C_9H_{12}N_4O$ requires C, 56·2; H, 6·3; N, 29·1), $\lambda_{max.}$ (in methanol) 218, 269, and 289 infl. mμ (ε 25,800, 5400, and 3300), $\lambda_{max.}$ (99% methanol and 1% N-sodium

hydroxide) 203, 230, 263 infl., and 297 infl. mμ (ε 24,400, 37,100, 2700, and 1600), $\nu_{max.}$ 1680 and 2650 cm.$^{-1}$. Identical products were obtained by isomerisation of the corresponding triazolo[4,3-*c*]pyrimidine (*a*), when a solution (from 0·25 g.) in N-sodium hydroxide (5 ml.) was kept for 16 hr. at 20°, and acetic acid was added to give colourless needles (15 mg.; m. p. 186—187°), and (*b*), when a solution (from 1 g.) in *o*-dichlorobenzene (45 ml.) and formic acid (0·4 ml.) was boiled under reflux for 2 hr. and evaporated to dryness, and the solid (m. p. 185—186°) was crystallised from ethanol. No isomerisation occurred when the formic acid was omitted. The same triazolo[2,3-*c*]pyrimidine (m. p. 186—187°) was also formed when 6-(4′-n-butylsemicarbazido)-4-methyl-2-n-propylpyrimidine (5 g.) in *o*-dichlorobenzene was boiled under reflux for 16 hr., and ethyl acetate was added to the syrup left by evaporation of the solvent. Crystallisation from light petroleum (b. p. 60—80°) of the residue left by evaporation of the ethyl acetate mother-liquor gave di-n-butylurea, m. p. and mixed m. p. 72—74° (Found: C, 62·9; H, 11·5; N, 16·3. Calc. for $C_9H_{20}N_2O$: C, 62·7; H, 11·7; N, 16·3%). In another experiment which finally gave the triazolo[2,3-*c*]pyrimidine, phosgene (3·3 g.) was passed into a solution of 6-hydrazino-4-methyl-2-n-propylpyrimidine (5 g.), dissolved in N-hydrochloric acid (30 ml.). After 0·5 hr., addition of sodium acetate (20 g.) and cooling to 0° gave a precipitate of a presumed *carbamic acid* which crystallised from water as colourless needles, m. p. 186—188° decomp. (Found: C, 51·6; H, 7·2; N, 26·5. $C_6H_{14}N_4O_2$ requires C, 51·4; H, 6·7; N, 26·6%), $\lambda_{max.}$ 215 infl., 235, and 287 mμ (ε 7000, 8000, and 16,700), $\nu_{max.}$ 1725s cm.$^{-1}$. This acid was converted into the 2-hydroxytriazolopyrimidine (m. p. and infrared) after being kept overnight at 20° in N-sodium hydroxide solution, followed by precipitation with glacial acetic acid.

2-*Bromo*-7-*methyl*-5-*n*-*propyl*-s-*triazolo*[2,3-c]*pyrimidine*. (*a*) 2-Hydroxy-7-methyl-5-n-propyl-*s*-triazolo[2,3-*c*]pyrimidine (2 g.) and phosphoryl bromide (10 g.) were heated together for 30 min. in a bath kept at 135—140°. The dark product was poured into a mixture of ice and excess of sodium carbonate, and the resulting suspension was extracted several times with ethyl acetate. Crystallisation from light petroleum (b. p. 60—80°) of the residue left by evaporation of the ethyl acetate gave the *triazolopyrimidine* as colourless needles, m. p. 86—88° (Found: C, 42·2; H, 4·1; N, 21·4. $C_9H_{11}BrN_4$ requires C, 43·4; H, 4·35; N, 22·0%), $\lambda_{max.}$ 213 and 254 mμ (ε 31,000 and 6200). (*b*) Bromine (2·1 ml.) was added dropwise to a solution of 2-amino-7-methyl-5-n-propyl-*s*-triazolo[2,3-*c*]pyrimidine (5 g.), in hydrobromic acid (9·3 ml., 48%) kept below 0°. Sodium nitrite (4·55 g.) in water (6 ml.) was added dropwise to the resultant paste, still below 0°. After 0·5 hr., the mixture was neutralised with concentrated aqueous sodium hydroxide below 25°. Ethyl acetate extraction and crystallisation as above gave the bromo-derivative (2 g., m. p. and mixed m. p. 88°).

2-*Ethoxy*-7-*methyl*-5-*n*-*propyl*-s-*triazolo*[2,3-c]*pyrimidine*. The 2-bromo-7-methyl-5-n-propyl-*s*-triazolo[2,3-*c*]pyrimidine (1 g.), in dry ethanol (15 ml.), was added to a solution of sodium (0·28 g.) in dry ethanol (15 ml.). The mixture was heated under reflux for 22 hr., and evaporated to dryness under reduced pressure. The residue left after treatment with cold water crystallised from light petroleum (b. p. 40—60°) to yield the *ethoxy-derivative* as very pale brown plates (0·15 g.), m. p. 49—50° (Found: C, 60·2; H, 7·2; N, 25·4. $C_{11}H_{16}N_4O$ requires C, 60·0; H, 7·3; N, 25·4), $\lambda_{max.}$ 214 and 258 mμ (ε 35,000 and 5000).

2-*Amino- and Substituted Amino*-s-*triazolo*[2,3-c]*pyrimidines made from* 2-*Bromo*-7-*methyl*-5-*n*-*propyl*-s-*triazolo*[2,3-*c*]*pyrimidine*.—The *compounds* listed in Table 2 were prepared by the action of the above bromotriazolopyrimidine (XIX) on the corresponding amine (2 or more mol.) in ethanol in a sealed tube at 150° for 48 hr.

s-*Triazolo*[2,3-c]*pyrimidines made by the Semicarbazide Route*.—2-*Amino*-7-*methyl*-5-n-*propyl*-s-*triazolo*[2,3-c]*pyrimidine*. 4-Methyl-2-n-propyl-6-semicarbazidopyrimidine (10·5 g.) in phosphoryl chloride (50 ml.) was heated under reflux for 2½ hr. Excess of phosphoryl chloride was distilled off under reduced pressure, and the residue was poured on ice. A small amount of orange solid was filtered off. The filtrate was neutralised with sodium acetate, extracted with chloroform, and the dried chloroform solution (magnesium sulphate) was concentrated, diluted with ether, and cooled in ice–water. The precipitated *product* crystallised from ethyl acetate (charcoal) as colourless plates (0·5 g.), m. p. 168—169°, undepressed with authentic 2-amino-7-methyl-5-n-propyl-*s*-triazolo[2,3-*c*]pyrimidine [1] (identical infrared absorption).

2-*Methylamino*-2-*methyl*-5-*n*-*propyl*-s-*triazolo*[2,3-c]*pyrimidine*. 4-Methyl-6-(4′-methylsemicarbazido)-2-n-propylpyrimidine (1·8 g.) was boiled under reflux with phosphoryl chloride (15 ml.) for 3 hr. Most of the excess of phosphoryl chloride was distilled off under reduced pressure, and the residue was poured on a mixture of ice and concentrated sodium hydroxide. The

resulting pale yellow precipitate was filtered off, washed with water, dried at 60°, and crystallised twice from ethyl acetate to yield the *triazolopyrimidine* as colourless needles, m. p. 121—122°, undepressed with authentic 2-methylamino-7-methyl-5-n-propyl-*s*-triazolo[2,3-*c*]pyrimidine [1] (identical infrared absorption).

2-*Ethylamino*-7-*methyl*-5-*n*-*propyl*-s-*triazolo*[2,3-c]*pyrimidine*. Similarly, 6-(4′-ethylsemicarbazido)-4-methyl-2-n-propylpyrimidine (8 g.) and phosphoryl chloride (40 ml.) gave the *triazolopyrimidine* as colourless needles (2·6 g.), m. p. 133—134°, when crystallised twice from ethyl acetate (Found: C, 60·2; H, 7·6; N, 31·4. $C_{11}H_{17}N_5$ requires C, 60·2; H, 7·8; N, 31·9%), $\lambda_{max.}$ 273 and 299 mμ (ε 41,800 and 3500).

2-*Allylamino*-7-*methyl*-5-*n*-*propyl*-s-*triazolo*[2,3-c]*pyrimidine*. Similarly, prepared from 6(4′-allylsemicarbazido)-4-methyl-2-n-propylpyrimidine (10 g.) and phosphoryl chloride (50 ml.), the crude *triazolopyrimidine* (6·3 g., m. p. 110°) crystallised from ethyl acetate as colourless plates (4·25 g.), m. p. 114° (Found: C, 62·6; H, 7·8; N, 30·4. $C_{12}H_{17}N_5$ requires C, 62·3; H, 7·4; N, 30·3%), $\lambda_{max.}$ 234 and 297 infl. mμ (ε 45,800 and 2400).

2-*n*-*Butylamino*-7-*n*-*heptyl*-5-*n*-*propyl*-s-*triazolo*[2,3-c]*pyrimidine*. Similarly, 6-(4′-n-butylsemicarbazido)-4-n-heptyl-2-n-propylpyrimidine (7 g.) and phosphoryl chloride (70 ml.), after decomposition of the reaction mixture and extraction with ethyl acetate, gave the *triazolopyrimidine* which crystallised from light petroleum (b. p. 60—80°) as colourless needles (2 g.), m. p. 63—64° (Found: C, 68·6; H, 10·1; N, 21·1. $C_{19}H_{33}N_5$ requires C, 68·8; H, 10·0; N, 21·1%), $\lambda_{max.}$ 235 and 303 mμ (ε 36,000 and 2500).

2-*Allylamino*-7-*methyl*-5-n-*pentyl*-s-*triazolo*[2,3-c]*pyrimidine*. Similarly, 6-(4′-allylsemicarbazido)-4-methyl-2-n-pentylpyrimidine (10 g.) and phosphoryl chloride (50 ml.) gave the *triazolopyrimidine* from light petroleum (b. p. 60—80°) as colourless needles, m. p. 90—91° (Found: C, 64·8; H, 8·2; N, 26·9. $C_{14}H_{21}N_5$ requires C, 64·8; H, 8·2; N, 27·0%), $\lambda_{max.}$ 234 and 297 mμ (ε 45,200 and 2200).

The above allyl derivative dissolved in ethanol (50 ml.) and reduced with hydrogen in the presence of platinum oxide (0·1 g.) gave 7-*methyl*-5-*n*-*pentyl*-2-*n*-*propylamino*-s-*triazolo*[2,3-c]-*pyrimidine* as colourless needles (1 g.), m. p. 88° from light petroleum (b. p. 60—80°) (Found: C, 64·7; H, 8·8; N, 26·8. $C_{14}H_{23}N_5$ requires C, 64·3; H, 8·9; N, 26·8%), $\lambda_{max.}$ 234 and 300 mμ (ε 43,500 and 2500).

2-*n*-*Butylamino*-5-*n*-*propyl*-7-*trifluoromethyl*-s-*triazolo*[2,3-c]*pyrimidine*. Similarly, 6-(4′-n-butylsemicarbazido)-2-n-propyl-4-trifluoromethylpyrimidine (2·3 g.) and phosphoryl chloride (10 ml.) gave the *triazolopyrimidine* from light petroleum (b. p. 60—80°) as colourless needles (1·6 g.), m. p. 104—105° (Found: C, 51·7; H, 6·6; N, 23·6. $C_{13}H_{18}N_5F_3$ requires C, 51·8; H, 6·0; N, 23·25%), $\lambda_{max.}$ 236, 271, and 316 mμ (ε 26,300, 2900, and 2800).

2-*Anilino*-7-*methyl*-5-n-*propyl*-s-*triazolo*[2,3-c]*pyrimidine*. Similarly, 4-methyl-6-(4′-phenylsemicarbazido)-2-n-propylpyrimidine (5 g.) and phosphoryl chloride (40 ml.) gave the *triazolopyrimidine* as a colourless microcrystalline solid (1·2 g.), m. p. 182—184° from ethanol (Found: C, 67·6; H, 6·5; N, 26·2. $C_{15}H_{17}N_5$ requires C, 67·4; H, 6·4; N, 26·2%), $\lambda_{max.}$ 209, 245, and 301 infl. mμ (ε —, 43,000, and 8500).

1,6-*Di*-(7-*methyl*-5-*n*-*propyl*-s-*triazolo*[2,3-c]*pyrimidinyl*-2-*amino*)-*n*-*hexane*. Similarly, the corresponding semicarbazide (4·4 g.) and phosphoryl chloride (25 ml.) gave the *triazolopyrimidine* as colourless microcrystals (1·05 g.), m. p. 155—156° from ethanol (Found: C, 62·05; H, 7·9; N, 29·75. $C_{24}H_{36}N_{10}$ requires C, 62·1; H, 7·75; N, 30·15%).

7-*Methyl*-2-*t*-*octylamino*-5-*n*-*propyl*-s-*triazolo*[2,3-c]*pyrimidine*. A preparation of the crude semicarbazidopyrimidine (5 g.) and phosphoryl chloride (50 ml.) were heated together under reflux for 3¼ hr. The solution was cooled, concentrated, and poured on a mixture of ice and excess of sodium hydroxide. Ethyl acetate extraction yielded a syrup which on crystallisation from a large volume of light petroleum (b. p. 60—80°) yielded colourless crystals, m. p. 166—168°, of 2-amino-7-methyl-5-n-propyl-*s*-triazolo[2,3-*c*]pyrimidine [1] (mixed m. p., infrared and ultraviolet absorption spectra). Concentration of the mother-liquors and crystallisation of the residue from light petroleum (b. p. 40—60°) gave the 2-*t*-*octylamino*-*triazolopyrimidine* as colourless plates (1·65 g.), m. p. 72—74° (Found: C, 67·5; H, 9·5; N, 23·0. $C_{17}H_{29}N_5$ requires C, 67·3; H, 9·6; N, 23·0%), $\lambda_{max.}$ 235 and 303 (ε 42,200 and 3300).

2-*n*-*Butylamino*-7-*methyl*-5-*n*-*propyl*-s-*triazolo*[2,3-c]*pyrimidine*. Similarly, 6-(4′-n-butylsemicarbazido)-4-methyl-2-n-propylpyrimidine (9 g.) and phosphoryl chloride (100 ml.) gave an ethyl acetate extract which on evaporation and crystallisation of the residue from light petroleum (b. p. 60—80°) yielded the *triazolopyrimidine* as colourless needles (2·25 g.), m. p.

84—85° (Found: C, 63·1; H, 8·4; N, 28·6. $C_{13}H_{21}N_5$ requires C, 63·1; H, 8·5; N, 28·3%), $\lambda_{max.}$ 233 and 301 mμ (ε 42,200 and 2800). The same product, m. p. 82—84° (no depression with above), was obtained (10 mg.) when the semicarbazidopyrimidine (2·5 g.), dry xylene (50 ml.), and phosphoric oxide (5 g.) were boiled under reflux for 70 min., and the sticky residue left after addition of ice and excess of sodium hydroxide was purified in like manner.

2-*Ethoxycarbonylmethylamino*-7-*methyl*-5-*n*-*propyl*-s-*triazolo*[2,3-c]*pyrimidine*. Similarly, 6-(4′-ethoxycarbonylmethylsemicarbazido)-4-methyl-2-n-propylpyrimidine (20 g.) and phosphoryl chloride (200 ml.) added to aqueous sodium carbonate after reaction and followed by extraction with ethyl acetate, gave the *triazolopyrimidine* from ethanol as colourless needles (2·2 g.), m. p. 139—140° (Found: C, 55·1; H, 6·4; N, 26·6. $C_{12}H_{17}N_5O_2$ requires C, 54·7; H, 6·5; N, 26·6%), $\lambda_{max.}$ 230, 258 infl., and 294 infl. mμ (ε 37,500, 4100, and 2200). The above ester (1 g.) heated under reflux with aqueous sodium hydroxide (4·2 ml., N) for 1 hr., acidified with N-hydrochloric acid to pH 4·5 and cooled to 0°, gave crude 2-*carboxymethyl*-7-*methyl*-5-*n*-*propyl*-s-*triazolo*[2,3-c]*pyrimidine* (0·5 g., m. p. 187—189°) which crystallised from ethanol as a colourless solid, m. p. 188—190°, freely soluble in cold aqueous potassium bicarbonate (Found: C, 52·8; H, 6·1; N, 27·8. $C_{11}H_{15}N_5O_2$ requires C, 53·0; H, 6·1; N, 28·1%), $\lambda_{max.}$ 234, 270 infl., and 304 mμ (ε 42,300, 3500, and 1800).

5,7-*Dimethyl*-2-*methylamino*-s-*triazolo*[2,3-c]*pyrimidine*. Similarly, 2,4-dimethyl-6-(4′-methylsemicarbazido)pyrimidine (9 g.) and phosphoryl chloride (90 ml.) (sodium carbonate neutralisation), gave the crude *triazolopyrimidine* (3 g., m. p. 171—172°) as the residue from evaporation of an ethyl acetate extract, which on crystallisation from ethanol yielded colourless prisms, m. p. 172° (Found: C, 54·3; H, 6·2; N, 39·4. $C_8H_{11}N_5$ requires C, 54·2; H, 6·3; N, 39·5%), $\lambda_{max.}$ 232, 260 infl., and 294 infl. mμ (ε 39,500, 3800, and 1800).

2-*Methylamino*-5,7-*di*-*n*-*propyl*-s-*triazolo*[2,3-c]*pyrimidine*. Similarly, 6-(4′-methylsemicarbazido)-2,4-di-n-propylpyrimidine (9 g.) and phosphoryl chloride (80 ml.) gave the triazolopyrimidine which crystallised from ether–light petroleum (b. p. 40—60°) (charcoal) as colourless needles (2 g.), m. p. 85—86° (Found: C, 61·6; H, 8·1; N, 30·1. $C_{12}H_{19}N_5$ requires C, 61·8; H, 8·2; N, 30·0%), $\lambda_{max.}$ 234, 261 infl., and 293 mμ (ε 44,300, 4200, and 2000). This compound afforded an *acetyl derivative*, m. p. 41—43° from light petroleum (b. p. 40—60°) (Found: C, 61·4; H, 7·9; N, 25·1. $C_{14}H_{21}N_5O$ requires C, 61·1; H, 7·7; N, 25·4%).

s-*Triazolo*[2,3-c]*pyrimidines made by the Thiosemicarbazide Route*.—2-*Amino*-7-*methyl*-5-*n*-*propyl*-s-*triazolo*[2,3-c]*pyrimidine*. The hydrochloride (5·05 g.) of 6-hydrazino-4-methyl-2-n-propylpyrimidine, prepared from the base (5 g.) and dry hydrogen chloride in ether, was heated under reflux for 2 hr. with ammonium thiocyanate (1·95 g.), in 2-ethoxyethanol (125 ml.). Filtration of the mixture after cooling, and evaporation of the solvent, left a yellow solid, which when ground under aqueous sodium acetate afforded crude 4-*methyl*-2-*n*-*propyl*-6-*thiosemicarbazidopyrimidine* (2·8 g., m. p. 212—216° decomp.). This product formed colourless microcrystals (m. p. 222—224° decomp.) from 2-ethoxyethanol (Found: C, 47·7; H, 7·1. $C_9H_{15}N_5S$ requires C, 48·0; H, 6·7%). A mixture of the thiosemicarbazide (1 g.), litharge (5 g.), and 2-ethoxyethanol (20 ml.) was boiled under reflux for 25 min. The suspension was filtered and the solvent removed under reduced pressure. The residue gave the *triazolopyrimidine* as colourless plates from ethyl acetate (150 mg.), m. p. 168—170° undepressed with authentic material.[1]

7-*Methyl*-2-*methylamino*-5-*n*-*propyl*-s-*triazolo*[2,3-c]*pyrimidine*. A mixture of 6-hydrazino-4-methyl-2-n-propylpyrimidine (5 g.) and methyl isothiocyanate (2·2 g.) in benzene (25 ml.) was boiled under reflux for 5 min. Addition of ether to the cooled solution gave a solid which afforded 4-*methyl*-6-(4′-*methylthiosemicarbazido*)-2-*n*-*propylpyrimidine* (4·3 g.) as a colourless solid, m. p. 174—175° decomp., from ethanol. Reaction of this (8·3 g.) with litharge (31 g.) as described above gave the *triazolopyrimidine* (0·5 g., m. p. 120—121°) as colourless needles from light petroleum (b. p. 60—80°). The product was identical with authentic material [1] (m. p., infrared and ultraviolet absorption spectra).

s-*Triazolo*[2,3-c]*pyrimidine by the* S-*Ethylthiosemicarbazide Route*.—2-*Amino*-7-*methyl*-5-*n*-*propyl*-s-*triazolo*[2,3-c]*pyrimidine*. Ethyl iodide (1 ml.) was added to a suspension of 4-methyl-2-n-propyl-6-thiosemicarbazidopyrimidine (2·25 g.) in boiling dry ethanol (50 ml., and the mixture was heated under reflux for 1 hr. The pale yellow solution was evaporated to dryness under reduced pressure and the residue was treated with aqueous sodium acetate. The supernatant liquid was decanted and the residual gum became solid after being ground under cold ethyl acetate. The hygroscopic product (1·1 g., m. p. 180—181° decomp.), which was assumed

to be a salt of the *S*-ethyl derivative of the thiosemicarbazidopyrimidine, was added to a suspension of litharge (5 g.) in boiling 2-ethoxyethanol (5 ml.). After 2½ min. the hot suspension was filtered and the solvent was evaporated to dryness under reduced pressure. The residue afforded 2-amino-7-methyl-5-n-propyl-*s*-triazolo[2,3-*c*]pyrimidine as colourless plates, m. p. 168—169°, from ethyl acetate, identical (m. p. and spectra) with authentic material.[1] The same product (0·2 g., m. p. 168—169°) resulted from the related reaction in which 6-hydrazino-4-methyl-2-n-propylpyrimidine (1·6 g.) was boiled under reflux in water (10 ml.) with *S*-methylisothiouronium sulphate (2·1 g.) for 16 hr. The crude product which separated on cooling was crystallised from ethyl acetate.

2-*Isobutylamino*-2-*methyl*-5-*n*-*propyl*-s-*triazolo*[2,3-c]*pyrimidine*. 6(4′-*Isobutylthiosemicarbazido*)-4-*methyl*-2-*n*-*propylpyrimidine* [(2 g.), prepared in 79% yield from isobutyl isothiocyanate and the hydrazinopyrimidine, m. p. 170° (Found: C, 55·3; H, 7·8. $C_{13}H_{23}N_5S$ requires C, 55·5; H, 8·2%) was converted into the *S*-ethylthio-derivative by the action of ethyl iodide (0·6 ml.)] in boiling ethanol (10 ml.). This product was treated with litharge as described above. The residue left after removal of the ethoxyethanol gave, with picric acid in ethanol, the *picrate of the triazolopyrimidine* which recrystallised from ethanol as yellow needles (0·45 g.), m. p. 176—177° (Found: C, 48·5; H, 4·9; N, 23·5. $C_{13}H_{21}N_5,C_6H_3N_3O_7$ requires C, 47·8; H, 5·1; N, 23·5%). An identical product was obtained in an experiment from which the litharge was omitted.

Amino-s-*triazolo*[2,3-c]*pyrimidines made by the Thiourea Method*.—6-*Cyanamido*-2,4-*dimethylpyrimidine*. A mixture of 6-chloro-2,4-dimethylpyrimidine (43 g.), sodium cyanamide (40 g.), and absolute ethanol (325 ml.) was heated under reflux for 63 hr. The cooled suspension was filtered and the solvent distilled off *in vacuo* from the filtrate. The residue was washed with light petroleum (b. p. 40—60°) to remove unchanged chloropyrimidine. It was then digested with water (100 ml.) at 50°, and the suspension was filtered. Addition of acetic acid to the filtrate at 0° gave the crude *cyanamide* which afforded colourless needles, m. p. 251—252°, from methanol (Found: C, 56·7; H, 5·5; N, 37·4. $C_7H_8N_4$ requires C, 56·7; H, 5·4; N, 37·8%), $\lambda_{max.}$ 208 and 293 mμ (ε 6100 and 16,900), $\nu_{max.}$ 2145s cm.$^{-1}$.

6-*Cyanamido*-4-*methyl*-2-*n*-*propylpyrimidine*. Similarly prepared from a mixture of 6-chloro-4-methyl-2-n-propylpyrimidine (30 g.) and sodium cyanamide (26 g.), heated together in dimethylformamide (200 ml.) for 40 hr. at 100°, and finally 2 hr. at 110°, the *cyanamide* crystallised from aqueous acetic acid as colourless plates (5 g.), m. p. 196—198° (Found: C, 60·6; H, 7·1; N, 31·5. $C_9H_{12}N_4$ requires C, 61·3; H, 6·9; N, 31·8%), $\lambda_{max.}$ 208 and 241 mμ (ε 12,000 and 33,000).

2,4-*Dimethyl*-6-*thioureidopyrimidine*. 6-Cyanamido-2,4-dimethylpyrimidine (2·5 g.) was heated in a sealed tube at 100° for 16 hr. with a saturated solution of hydrogen sulphide in a mixture of ammonium hydroxide (2 ml., *d* 0·88) and water (10 ml.). The precipitate which formed on cooling was filtered off, washed with ice–water and crystallised from aqueous ethanol to yield the *thioureidopyrimidine* as colourless needles (2 g.), m. p. 242° (Found: C, 46·2; H, 5·6; N, 30·8. $C_7H_{10}N_4S$ requires C, 46·15; H, 5·5; N, 30·7%), $\lambda_{max.}$ 207, 238, and 291 mμ (ε 9800, 9300, and 26,900).

2-*Amino*-5,7-*dimethyl*-s-*triazolo*[2,3-c]*pyrimidine*. Hydrazine hydrate (1·25 ml., 100%) was added to a solution of 2,4-dimethyl-6-thioureidopyrimidine (1 g.) dissolved in hot 2-ethoxyethanol (15 ml.). The mixture was heated under reflux for 16 hr. and then cooled to 0°. A white precipitate gradually separated. The solid residue which remained after filtration and concentration of the filtrate formed colourless needles, m. p. 250—251°, from ethanol, of 2-amino-5,7-dimethyl-*s*-triazolo[2,3-*c*]pyrimidine identical with authentic material [1] (m. p., infrared and ultraviolet spectra).

4-*Amino*-4-*ethyl*-2,6-*di*-n-*propylpyrimidine*. A mixture of sodium methoxide [from sodium (11 g.) dissolved in methanol] and dry n-butyronitrile (43·5 g.) was stirred and heated in an autoclave at 180° (±5°) for 12 hr. The resultant paste was treated with water (300 ml.), and sufficient concentrated hydrochloric acid was added to give acidity. The solution was extracted with ether, and the aqueous layer, after warming under reduced pressure to remove dissolved solvent, was chilled and made strongly alkaline with an excess of sodium hydroxide. The crude aminopyrimidine which separated was filtered off, washed with a little cold water, and air-dried (20·5 g., m. p. 109—111°). Crystallisation from water gave material of m. p. 114°. Schwarze [4] gives m. p. 114°.

[4] R. Schwarze, *J. prakt. Chem.*, 1890, **42**, 4.

2-*Methylamino*-4-*ethyl*-5,7-*di*-n-*propyl*-s-*triazolo*[2,3-c]*pyrimidine*. The gummy residue of the crude methylthioureidopyrimidine left after removal of excess of methyl isothiocyanate from a reaction in which the latter (1·2 g.) was heated in a sealed tube at 150° for 12 hr. with 4-amino-5-ethyl-2,6-di-n-propylpyrimidine (2·3 g.), was dissolved in 2-ethoxyethanol (10 ml.) containing hydrazine hydrate (5 ml.). Litharge (10 g.) was added, and the mixture was boiled gently for 5 min. and filtered. The residue which remained after evaporation of the solvent *in vacuo* was digested with water and sufficient 2N-hydrochloric acid added to give pH 2—3. The fine crystalline suspension was filtered to give the *triazolopyrimidine* (0·9 g., m. p. 106°) which recrystallised from methanol (charcoal) in colourless needles, m. p. 106° (Found: C, 64·0; H, 8·8; N, 26·1. $C_{14}H_{23}N_5$ requires C, 64·4; H, 8·8; N, 26·8%).

2-*Methylamino*-5,7-*dimethyl*-s-*triazolo*[2,3-c]*pyrimidine*. Similarly prepared from the corresponding methylthioureidopyrimidine (5·1 g., see below), the residue, after removal of the 2-ethoxyethanol, gave colourless rectangular prisms of the *triazolopyrimidine* (2 g.), m. p. 171—172°, from ethanol (Found: C, 54·2; H, 6·3; N, 39·5. $C_8H_{11}N_5$ requires C, 54·25; H, 6·2; N, 39·55%). The 2,4-*dimethyl*-6,3′-*methylthioureidopyrimidine* required in this experiment was prepared from methyl isothiocyanate (2·2 g.) and 6-amino-2,4-dimethylpyrimidine (2·5 g.) heated together in a sealed tube in *o*-dichlorobenzene (5 ml.) at 150° for 2 hr. It formed colourless prismatic needles, m. p. 157—158°, of a *hemihydrate* from aqueous ethanol (Found: C, 47·0; H, 6·4; N, 26·4; S, 15·7. $C_{18}H_{12}N_4S,\frac{1}{2}H_2O$ requires C, 46·8; H, 6·35; N, 27·3; S, 15·6%).

2-*n-Butylamino*-5,7-*dimethyl*-s-*triazolo*[2,3-c]*pyrimidine*. Similarly prepared from the corresponding butylthioureidopyrimidine (2·3 g.), the crude product after removal of 2-ethoxyethanol was shaken with cold light petroleum (b. p. 60—80°) and water, with the addition of sufficient 2N-sulphuric acid to give pH *ca.* 3. This left the weakly basic *triazolopyrimidine* (0·95 g., m. p. 100—101°) as a crystalline solid, which was recrystallised from light petroleum (b. p. 60—80°) as colourless needles, m. p. 100—101° (Found: C, 60·5; H, 7·8; N, 32·3. $C_{11}H_{17}N_5$ requires C, 60·3; H, 7·7; N, 32·0%). The 6-3′-*n-butylthioureido*-2,4-*dimethylpyrimidine* required for this experiment was made from n-butyl isothiocyanate (5·2 g.), and the aminodimethylpyrimidine (3·7 g.), heated together at 165—176° for 2 hr. The crude product (3·4 g., m. p. 111—113°) left after addition of light petroleum (b. p. 40—60°) to the cooled melt, gave colourless needles (1·85 g.), m. p. 133—134°, from light petroleum (b. p. 100—120°) (Found: C, 55·8; H, 7·9; N, 22·8; S, 13·5%. $C_{11}H_{18}N_4S$ requires C, 55·45; H, 7·55; N, 23·5; S, 13·45%).

Action of Cyanogen Chloride on 4-*Amino*-2,6-*dimethylpyrimidine*.—Cyanogen chloride (4·6 g.) was bubbled slowly into 4-amino-2,6-dimethylpyrimidine in water (40 ml.) at 0—5°. Sodium hydrogen carbonate (8·4 g.) was added cautiously to the solution. After 1½ hr., the resultant precipitate was filtered off, washed with water, and dried *in vacuo*. The *product*, which was soluble in cold dilute sodium hydroxide, formed colourless microcrystals which when heated changed their physical form at 154° and melted at 248° (Found after drying *in vacuo* over P_2O_5: C, 50·3; H, 6·0; N, 33·2. $C_7H_{10}N_4O$ requires C, 50·6; H, 6·0; N, 33·7%), $\nu_{max.}$ 3350vs, 2170vs, and 1710s cm.$^{-1}$.

A solution of the above compound (0·5 g.) in water (40 ml.) kept at the boil for 2 min. and then cooled, yielded the supposed *acetamidopyrimidine* (XIe), m. p. 261—262° (Found after drying *in vacuo* at 115°: C, 50·7; H, 6·2; N, 33·3. $C_7H_{10}N_4O$ requires C, 50·6; H, 6·0; N, 33·7%), $\nu_{max.}$ 1700vs cm.$^{-1}$ (in dimethyl sulphoxide). A solution of this compound (1 g.), in 2N-sodium hydroxide (10 ml.), was kept at the boil for 2 min., cooled, and treated with more sodium hydroxide (10N; 10 ml.) whereupon 2,4-diamino-6-methylpyrimidine (0·65 g.) was precipitated. The base formed prismatic needles (m. p. and mixed m. p. 185—186°; infrared spectra identical with authentic specimen) from acetone (Found: C, 48·8; H, 6·6; N, 44·5. Calc. for $C_5H_8N_4$: C, 48·4; H, 6·45; N, 45·1%).

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