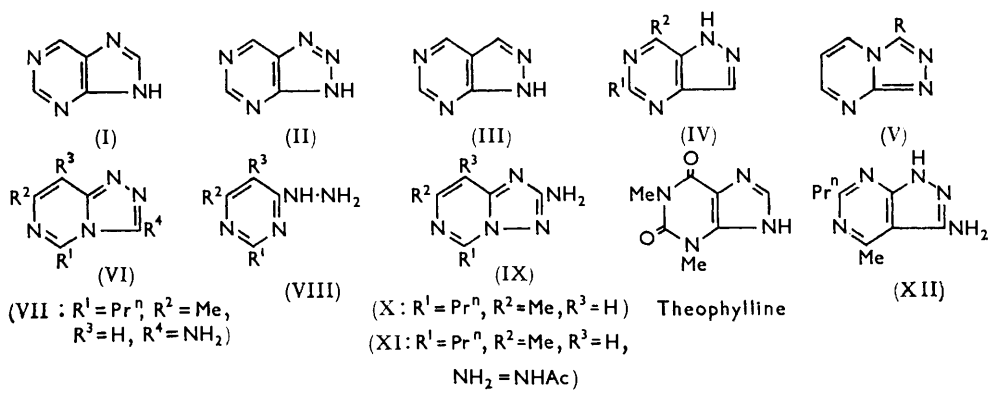
1080. s-*Triazolopyrimidines. Part I. Synthesis as Potential Therapeutic Agents.*

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

The interaction of cyanogen chloride and 4-hydrazinopyrimidines under mild conditions yields 3-amino-*s*-triazolo[4,3-*c*]pyrimidines which are isomerised by heat or strong alkali or acids to the corresponding 2-amino-*s*-triazolo[2,3-*c*]pyrimidines (IX). Members of the latter series containing alkyl groups in the pyrimidine ring are potent bronchodilators.

The preparation of bicyclic structures isosteric with and chemically related to the naturally occurring purines has become a fertile source for the discovery of novel substances showing a wide variety of biological effects. The chemical devices used have ranged from the introduction of " unnatural " substituents into the purine nucleus itself (I), through the replacement of nuclear –CH= units by nitrogen atoms [*e.g.*, (II)], to a rearrangement of the normal components of one or other of the ring systems to give, for example, the pyrazolopyrimidines (III) and (IV). The last-named type has been the subject of earlier investigations by one of the present authors, and yielded a compound (IV; $R^1 = NH_2$, $R^2 = Me$) having marked antituberculous activity in experimental infections.[1]

A further possible structural variation arises, in effect, from rotation of the pyrimidine nuclei of either (III) or (IV) to give the triazolopyrimidines (V) and (VI), and substances of both types have already been described. The former has been studied for use in photographic chemistry in this country and in U.S.A.,[2] and by Sirakawa in Japan.[3] By contrast the isomeric type (VI) has been but little investigated.[4–6] In our hands, it has proved to have the greater biological interest, and it forms the basis of most of the work that it is proposed to recount in the present series of papers.



The greater part of these researches has concerned the 3-amino-*s*-triazolo[4,3-*c*]-pyrimidines (VI; $R^4 = NH_2$) to which we were particularly attracted by their potential

[1] Rose, *J.*, 1952, 3448.
[2] (*a*) Allen *et al.*, *J. Org. Chem.*, 1959, **24**, 779, 787, 793, 796; 1960, **25**, 361; (*b*) Williams, *J.*, 1960, 1829; 1961, 3046.
[3] Sirakawa, *J. Pharm. Soc. Japan*, (*a*) 1958, **78**, 1395; (*b*) 1959, **79**, 899; (*c*) 1959, **79**, 903, 1482, 1487; (*d*) 1960, **80**, 952, 956, 1550; (*e*) Jap. Patent 3326/1959 (*Chem. Abs.*, 1960, **54**, 14,278c).
[4] (*a*) Shiho *et al.*, *J. Pharm. Soc. Japan*, 1956, **76**, 804 (*Chem. Abs.*, 1957, **51**, 1196g); (*b*) Bower and Doyle, *J.*, 1957, 727; (*c*) Camerino *et al.*, *Gazzetta*, 1960, **90**, 1821, 1830; (*d*) Glässer, *Arch. int. Pharmacodyn. Thérapie*, 1960, **124**, 375.
[5] Potts, *Chem. Rev.*, 1961, **61**, 87.
[6] Mosby, " Heterocyclic Systems with Bridgehead Nitrogen Atoms," Interscience Publ. Inc., New York, 1961, p. 878.

availability through reaction of the corresponding hydrazinopyrimidines (VIII) with cyanogen halides. References [7] to the action of these agents on hydrazines gave the impression that cyanohydrazines were produced initially but were liable to undergo secondary reactions such as the formation of benzimidazole derivatives from phenylhydrazine and cyanogen bromide.[8] It was to be expected therefore that under mild conditions the hydrazine (VIII) would behave similarly and that the labile cyanohydrazinopyrimidine could then be cyclised to the triazolopyrimidine (VI). In fact, in no case has the intermediate been isolated, so facile was the subsequent ring-closure. At an early stage an additional complication was encountered arising from the formation, sometimes in the course of the primary reaction with cyanogen chloride, of isomeric substances which are now known to be the corresponding 2-amino-s-triazolo[2,3-*c*]pyrimidines (IX). Subsequent studies have enabled us to define the precise circumstances under which isomerisation could occur, and which we have shown to differ according to the nature of the substituent groups of the pyrimidine nucleus. The least complicated systems were those in which the groups were alkyl. This series also included the compounds of greatest biological interest, when it was observed by our colleague Mr. G. E. Davies that substances of type (IX; $R^1 = R^2 =$ alkyl), and in particular (X), exhibited some of the useful pharmacological properties of theophylline, but to a much greater degree. The triazolopyrimidine (X), for example, was shown to protect guinea pigs from the lethal effects of a histamine spray at doses one-hundredth of those required with the alkaloid. The bronchodilatory action *in vivo* still persisted in the acylamino-derivatives which were preferred on the grounds of toxicity, and these have additionally been the subject of further chemical investigation. It is tempting to suggest that the theophylline-like activities of this series of compounds are dependent in some measure upon the obvious structural resemblance to the naturally occurring compound, particularly in respect of the orientation of the two alkyl groups in relation to the bicyclic system.

All the hydrazinopyrimidine intermediates described in this Part were prepared by the reaction of alcoholic hydrazine hydrate in excess with the corresponding chloropyrimidines. A deficiency of hydrazine led to the expected formation of dipyrimidinylhydrazines. 4-Hydrazino-2,6-dimethylpyrimidine was additionally obtained by the reaction of the 4-aminopyrimidine with hydrazine, a replacement which failed with the higher homologue 4-amino-5-ethyl-2,6-di-n-propylpyrimidine. The chloropyrimidines were themselves prepared by the action of phosphoryl chloride on the corresponding hydroxypyrimidines, which in turn were available by slight modification of Pinner's method from amidines and β-keto-esters. The first reactions between the hydrazinopyrimidines and cyanogen chloride were carried out at 25—30° in dilute hydrochloric acid, in which all the hydrazines were readily soluble. The products were isolated by addition of sodium acetate and it was subsequently found that they were invariably the triazolo[2,3-*c*]pyrimidines. Even when the reaction was effected in dilute aqueous acetic acid containing sodium acetate as buffer, and at temperatures as low as 5—10°, considerable amounts of these particular isomers were frequently produced. As was expected, cyanogen bromide could be used in place of cyanogen chloride. On the other hand, the use of aqueous alcohol as solvent, and sodium carbonate as acid-binding agent, allowed the 4,3-*c* isomers to be isolated. The assignment of one isomeric structure or the other to the many hundreds of triazolopyrimidines prepared during the course of this investigation has been a matter of considerable labour, and not unexpectedly has left unsolved problems. In the case of the 2,3-*c* isomers, the circumstantial evidence arising from the many alternative routes to their synthesis will be described in subsequent communications. The biologically important compound (X) has been the object of especial study. For example, its precise molecular configuration

[7] Migrdichian, " The Chemistry of Organic Cyanogen Compounds," Reinhold Publ. Corp., 1947, p. 104.
[8] Pellizzari and Gaiter, *Gazzetta*, 1918, **48**, II, 151.

has been established for us by our colleagues Drs. Owston and Rowe, using *X*-ray crystallographic techniques which have been described elsewhere.[9] The hydrochloride was chosen in order to provide a suitable marker atom, and we checked that it was readily reconverted into the parent base by aqueous sodium acetate, or even water alone, at room temperature. In summary, the measurements obtained (Fig. 1) have proved conclusively that compound (X) has the structure shown, and not (VII) as was originally supposed, but it was not possible to distinguish absolutely between carbon and nitrogen atoms. Each of the two fused rings is almost exactly planar, indicating that the bonds have considerable aromatic character, and the two planes are inclined at an angle of 6° to one another. The bond-lengths in the fused ring system are all considerably less than normal single-bond lengths, but simple resonance theory is inadequate to explain them. In fact they appear more as conjugated double and single bonds. The structure found bears considerable

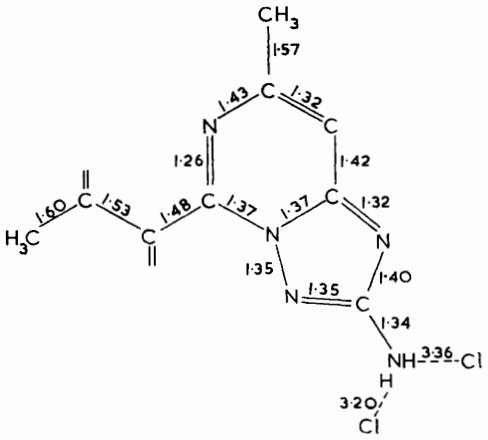


FIG. 1. Configuration of compound (X) determined by *X*-ray crystallography.

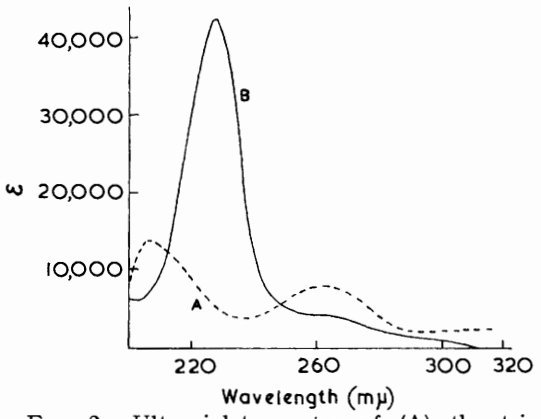


FIG. 2. Ultraviolet spectra of (A) the triazolo[4,3-*c*]pyrimidine (VII) and (B) the triazolo[2,3-*c*]pyrimidine (X) in MeOH

resemblance to that of caffeine.[10] The molecules are linked by a spiral chain of bonds 3·18 and 3·3 Å long between the chloride ion and the primary amino-group, implying the existence of hydrogen bonds, and by other bonds 3·29—3·5 Å long. There is no direct evidence to show the positions of the hydrogen atoms, apart from those in the alkyl side-chains, but since the co-ordination round the exocyclic nitrogen atom is planar, it can be inferred that the proton is probably attached to a ring-nitrogen atom. The results of these studies also excluded another possible but most unlikely structure for (X), that of the pyrazolopyrimidine (XII), although circumstantially this had been disposed of already by comparison with the substances derived from the material (VIII; R^3 = alkyl) which could not ring-close in this way, by studies with nuclear magnetic resonance, and by degradation of compound (X) to an *s*-triazolo-derivative (see below). The last piece of evidence is regarded as decisive proof for structure (X). Since the other members of this series shown in Table 4 were prepared in the same way as compound (X) and have similar chemical and physical properties, they are also regarded as 2-amino-*s*-triazolo[2,3-*c*]-pyrimidines.

No rigid proof such as that presented by *X*-ray data was available for the structure of the supposed 4,3-*c* isomers and indirect evidence must be accepted. Thus the isomer (VII), corresponding to (X), like (X) itself, showed prominent absorption bands in the infrared spectrum corresponding to the NH_2 region, although the possibility of these being due to –NH·NH– could not be excluded; and there was no absorption in the nitrile region, where

[9] Owston and Rowe, *Acta Cryst.*, 1962, **15**, 231.
[10] Sutor, *Acta Cryst.*, 1958, **11**, 453.

it would have been expected if the compound had possessed an acyclic cyanohydrazinopyrimidine structure. The pattern of absorption in the " ring-band " (6—7 μ) region was characteristic and clearly distinguishable from that of the 2,3-*c* series. Under mild conditions, compound (VII) and its congeners reacted with nitrous acid to give solutions which developed intense colours with alkaline R-salt. The 2,3-*c* derivatives behaved similarly, but the coloration was less intense. In both cases, this was probably due to the presence of an amino-group capable of diazotisation, such as is known to occur in the closely related amino-*s*-triazoles, although an acid-labile cyanohydrazinopyrimidine might perhaps behave similarly.

The ultraviolet absorption spectra of compound (VII) and its relatives were entirely different from those of the 2,3-*c* isomers (Fig. 2). Absorption by the former occurred at longer wavelengths and the individual peaks were much less intense. It is not unlikely that the isomeric hypothetical cyanohydrazinopyrimidine would absorb similarly, were it available for examination. The spectra of the members of the 2,3-*c* series were quite distinctive, and characteristically more compact.

On prolonged boiling with salicylaldehyde in ethanol both compounds (VII) and (X) gave Schiff bases, presumably (XIII) and (XIV), respectively, which differed from one another, not only in melting point, but also in that the base (XIII) absorbed at longer wavelengths, in the visible region. The infrared spectrum of isomer (XIV) did not reveal a hydroxyl group, but since the compound was highly soluble in dilute aqueous sodium hydroxide to give a bright yellow solution, it was presumed that such a group was present but masked in the solid state. Evidence from diazotisation suggested that the aldehyde residue was removed by warming the anil (XIV) in dilute hydrochloric acid. Catalytic reduction gave what was assumed to be the corresponding 2-hydroxybenzylaminotriazolopyrimidine. No Schiff base could be obtained, under the same conditions, from compound (X) and *p*-anisaldehyde or *p*-dimethylaminobenzaldehyde, but compound (VII; $R^1 = Bu^t$, $R^2 = Me$, $R^3 = H$, $R^4 = NH_2$), a homologue of (VII), gave a 4-methoxybenzylidene derivative of undetermined configuration when kept with the aldehyde in cold glacial acetic acid. Chloral and compound (X) in dioxan readily gave an addition product which was presumed to carry the group $-NH\cdot CH(OH)\cdot CCl_3$ on account of the close similarity of the infrared, and particularly the ultraviolet, absorption spectra to those of the amine (X) itself.

Because of the possible therapeutic implications, the amine (X) was subjected to more extensive chemical and physical studies than its less stable isomer. Thus, numerous salts were prepared. For the most part they dissociated in water with precipitation of the base, in line with the pK_a of 2·45 determined for the latter. With the discovery of equal biological activity *in vivo* in its acetyl derivative (XI) and preference of this derivative for possible clinical trial, this substance was investigated fully, and many more related amides were prepared. The amide (XI) was prepared by the action of acetic anhydride on the base. It was soluble in dilute aqueous sodium hydroxide (precipitated unchanged by acid), and treatment of the solution so obtained with dimethyl sulphate gave a methylated derivative. These observations were taken to support the presence of the acetyl group on the exocyclic nitrogen atom, *i.e.*, that of the amino-group. Further support for this view has come from comparison of the ultraviolet absorption spectra of the base and the amide, and from the infrared spectrum of the latter.

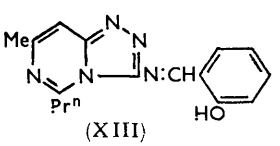
The corresponding stearoyl derivative, from the amine and the acid chloride in pyridine, was sufficiently soluble in chloroform for studies on infrared absorption and nuclear magnetic resonance to be made in solution. Results from both techniques favoured the presence of the acyl residue on the 2-amino-group. By analogy with these results the other acyl derivatives mentioned below are also regarded as 2-acylamino-derivatives. The formyl derivative resulted from refluxing the base in formic acid. Standard methods were also used to prepare the higher alkyl analogues. Benzoylation under Schotten–Baumann conditions failed, but succeeded in the presence of pyridine in place of sodium

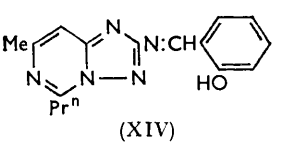
hydroxide. Maleic anhydride in dioxan gave the maleamic acid. Several attempts to effect the related reaction with succinic anhydride were unsuccessful but the succinamic acid was obtained by catalytic reduction of the maleic derivative. Phthalic anhydride gave the phthalimide, and such a structure is only likely on the assumption that the 2-amino-nitrogen is acylated. Finally, a tosyl derivative was prepared.

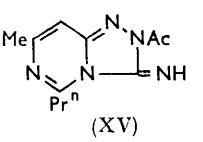
The acetamide (XI) was readily deacetylated by either acid or alkali to give the parent amine (X). Since this amide has little activity *in vitro* its high activity *in vivo* in the guinea pig is presumably due to metabolic deacetylation. The phthaloyl and the tosyl derivative, both of which have little activity *in vivo* (in the guinea pig), are relatively resistant to acid hydrolysis.

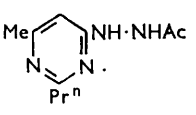
Acylations involving the 4,3-*c* isomers clearly ran the risk of associated isomerisation, but our colleagues A. F. Crowther, W. Broadbent, and L. H. Smith have studied the problem and have shown that, provided the medium is kept alkaline, compound (VII), for example, can be converted into an acetyl derivative which from its infrared and nuclear magnetic resonance spectra was assumed to have the structure (XV). The production of the same compound by these workers through the action of cyanogen chloride on the acethydrazide (XVI) confirmed this view. Unlike the amide (XI), the isomeric acetyl derivative (XV) is not soluble in cold dilute sodium hydroxide, again in accord with expectation.

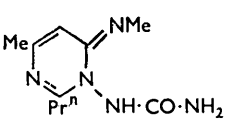
Methylation of the amide (XI) under alkaline conditions, to give a derivative of fairly certain structure, has already been mentioned. The base (X) itself was recovered unchanged after treatment with methyl iodide for two days in methanolic potassium carbon-

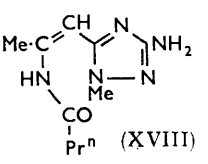

(XIII)

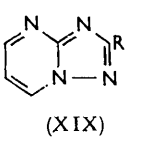

(XIV)


(XV)


(XVI)


(XVII)

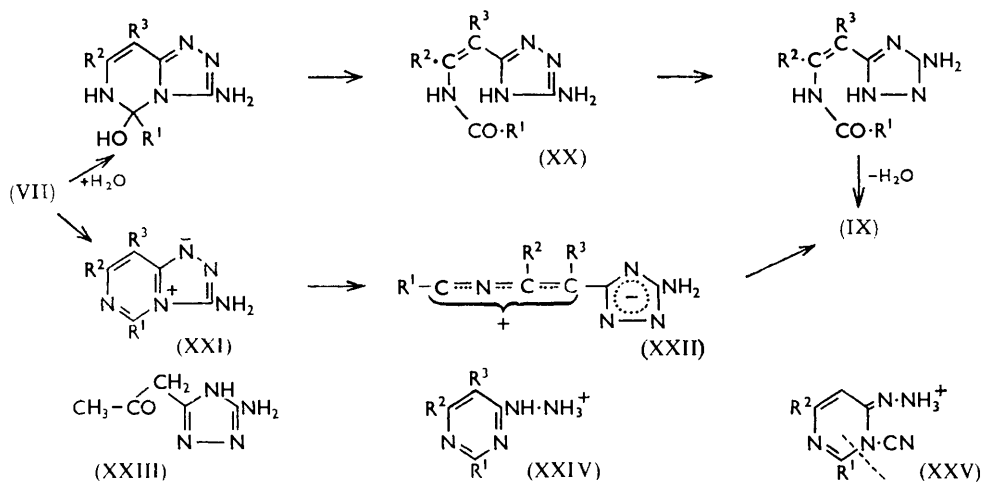

(XVIII)


(XIX)

ate, but dimethyl sulphate in nitrobenzene at 140° gave a presumed quaternary methosulphate which when added to aqueous sodium bromide gave a methobromide. Sodium iodide similarly formed the methiodide. The latter when dissolved in warm water and made strongly alkaline with sodium hydroxide gave a crystalline base having analyses for $C_{10}H_{17}N_5O$ even after drying at 100° *in vacuo*. The sparing solubility of this compound in water suggested that it was unlikely to be a quaternary ammonium hydroxide, and in any event the ultraviolet absorption spectrum was unlike that associated with any triazolopyrimidine and therefore quite different from that of the parent methiodide. Likewise the failure to form an anhydro-base on drying excluded both position 3 and the nitrogen atom of the primary amino-group as points of entry for the methyl group. The latter position was also excluded by the non-identity of the product with the 2-methylamino-derivative whose unambiguous synthesis will be described in a later contribution. Hydrolysis of one or other of the hetero-rings remained as the most likely possibility and (XVII) and (XVIII) are suggested as possible structures. Preliminary attempts to distinguish between compounds with intact pyrimidine and *s*-triazole rings are mentioned in the Experimental section.

There remains to discuss the occurrence of both 4,3-*c* and 2,3-*c* isomers, and the conversion of the one into the other. While this research was in progress, studies by the Kodak

group of workers [2] began to appear concerning the phenomenon observed by them, and also by Sirakawa,[3] of the reactions whereby the closely related triazolo[4,3-*a*]pyrimidines (V) can be isomerised to the corresponding triazolo[2,3-*a*]pyrimidines (XIX). In contradistinction to the 2,3-*c* series, the latter isomers were also available directly through condensation of 3-amino-*s*-triazoles with β-dicarbonyl compounds. These studies have already been adequately summarised by Potts [5] and Mosby.[6] In general, the R substituents in the compounds of type (V) and (XIX) described by these workers have been hydrogen or hydrocarbon radicals, and have been introduced by treatment of the corresponding 2-hydrazinopyrimidines with acylating agents, *e.g.*, formic acid (R = H), often under comparatively severe experimental conditions which made it difficult for them to determine whether ring-closure had or had not been accompanied by isomerisation. The especial virtue of methods involving cyanogen chloride, and which incidentally we have applied to the 2-hydrazinopyrimidine series to be described in a later communication, arose from the greater chemical reactivity of this agent, whereby the condensations could be brought about under the mildest conditions. This facilitated the study of the conversion (VI) ⟶ (IX) as a distinct issue, and in general we have found that any departure in handling solutions away from approximate neutrality, particularly in water or alcohol, brings the change about. It is expedited by higher temperatures, and indeed in several cases mere heating with or without a solvent has itself resulted in isomerisation. In line with the mechanistic hypotheses advanced to explain the phenomenon in the 4,3-*a* series, it seems reasonable to suppose that in the presence of water an intermediate open-chain structure is involved. Alternatively, it is unnecessary to postulate the actual intervention of the " open-chain " compound (XX) as an entity, especially when explaining the occurrence of the isomerisation due to heat alone, and its place could be taken by a reactive zwitterionic intermediate state (XXII) brought about by the rupture of the 4,5-bond in the limiting state (XXI), as proposed by Sirakawa [3a] for the 4,3-*a* series. The catalytic action of hydroxyl or hydrogen ions can then be explained as a stabilisation of either the cationic or the anionic portions of species (XXII), an effect which, however caused, would be



expected to facilitate the conversion of one isomer into the other. Support for this view arises from the fragmentation reactions that have been observed either during the course, for example, of acid-induced isomerisation, or as a result of hydrolytic breakdown of preformed triazolo[2,3-*c*]pyrimidines. Such reactions would be favoured by the capacity of the triazole system in the intermediate (XXII) to donate electrons to the side-chain. Thus it was observed that the yield of compound (IX; R^1 = Bu^t, R^2 = Me, R^3 = H)

obtained directly by the action of cyanogen chloride on the hydrazine (VIII; $R^1 = Bu^t$, $R^2 = Me$, $R^3 = H$) dissolved in cold dilute hydrochloric acid is particularly poor, and pivalamide was isolated in substantial yields when compound (VI; $R^1 = Bu^t$, $R^2 = Me$, $R^3 = H$, $R^4 = NH_2$) was kept for 65 hours in ~2·5N-hydrochloric acid at laboratory temperature, although with N-acid a certain amount of the 2,3-*c* isomer was isolable after a short period. The other organic residue was a substance $C_5H_8N_4O$, isolated first as a hydrated hydrochloride and as a picrate. The steric influence of the t-butyl group would be expected to exaggerate fragmentation in this manner, but similar hydrolytic phenomena have been seen under more drastic conditions with compound (X), which when refluxed with dilute hydrochloric acid gave butyric acid, ammonium chloride, and the salt of the same base. The last-named compound was eventually isolated and characterised as the free base. It was shown to exhibit an infrared band at 1708 cm.$^{-1}$ and formed a *p*-nitrophenylhydrazone having an ultraviolet absorption spectrum closely resembling that of the hydrazone from acetone. The alkaline nitroprusside reaction strongly suggested a $CO{\cdot}CH_2$ group, and a positive iodoform reaction (smell only) was indicative of the presence of $Me{\cdot}CO^-$. The base could be diazotised and coupled, and this together with the low level of absorption in the ultraviolet region lent support to structure (XXIII) for the compound. So far, attempts to reduce it to the known 5-amino-3-n-propyl-*s*-triazole have failed.

One further point remains for comment in connection with the isomerisation. The yields of the 2,3-*c* isomers obtained by the " direct " route, that is, by treatment of the hydrazinopyrimidines with cyanogen chloride in dilute hydrochloric acid, were often substantially higher than would be expected from the comparable yields obtained by acid isomerisation of the corresponding 4,3-*c* isomers. This has led us to suggest that in certain instances protonation of the hydrazinopyrimidines in acid solution occurred preferentially, as might be expected, on the terminal nitrogen atom of the hydrazine residue (XXIV). This would inhibit cyanation at this position, which might then take place on the adjacent ring nitrogen as shown in (XXV). Fission of the pyrimidine nucleus at the point indicated, followed by closure of the stable aminotriazole ring, and then re-formation of the pyrimidine ring on N-2 of the latter, would account for the production of the 2,3-*c* isomer without the intervention of a 4,3-*c* stage. No direct experimental evidence has been sought for this hypothesis, but reactions involving the attack of pyrimidine-nitrogen atoms by the cyano-group will be mentioned in another connection in a later communication.

Experimental

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

Cyanogen chloride was used from a cylinder and bubbled through water. All such operations were performed in an efficient fume-cupboard. Great care was always taken when working with this highly toxic compound.

Ultraviolet spectra were usually determined for solutions in redistilled methanol, with an " Optica " CF4 DR spectrophotometer. The curves shown in Fig. 2 were determined with an " Optica " CF4 manual spectrophotometer.

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

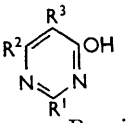
6-Hydroxypyrimidines were prepared by a slight modification, of which the following is typical, of Pinner's process.[11]

4-Hydroxy-6-methyl-2-n-propylpyrimidine.—Sodium (105 g.) in methanol (1200 ml.) was added slowly to a stirred solution of butyramidine hydrochloride (262 g.) and ethyl acetoacetate (278 g.) in methanol (600 ml.), below 10°. The mixture was stirred under reflux for 16 hr., then evaporated to dryness under reduced pressure. The residue was dissolved in the

[11] Pinner, (*a*) *Ber.*, 1889, **22**, 1616; (*b*) *Ber.*, 1885, **18**, 2847; (*c*) " Die Imidoäther und ihre Derivate," Berlin, 1892, p. 227.

TABLE 1.

Hydroxypyrimidines.



			Yield	Found (%)				Required (%)			
R^1	R^2	R^3	(%)	C	H	N	Formula	C	H	N	M. p., etc.
Me	Me	H	83	—	—	—	$C_6H_8N_2O$ *	—	—	—	196—198° ‡
Et	,,	,,	75	61·3	7·4	20·5	$C_7H_{10}N_2O$ †	60·85	7·3	20·3	Needles,[1] 162—164°
n-C_5H_{11}	,,	,,	95	66·7	8·9	15·4	$C_{10}H_{16}N_2O$	66·65	8·95	15·55	Needles,[2] 80—81°
Et	Et	,,	55	62·8	7·9	18·3	$C_8H_{12}N_2O$	63·15	7·95	18·4	Needles,[2] 89—90°
,,	Pr^n	,,	38	64·3	8·4	17·0	$C_9H_{14}N_2O$	65·05	8·5	16·85	Needles,[3] 67—68°
Pr^n	,,	,,	63	65·9	8·4	15·1	$C_{10}H_{16}N_2O$	66·65	8·95	15·55	Needles,[4] 71—73°
,,	Bu^n	,,	65	67·0	9·2	13·8	$C_{11}H_{18}N_2O$	68·0	9·35	14·4	63—65° [4]
,,	Me	Allyl	59	68·8	8·4	13·9	$C_{11}H_{16}N_2O$	68·7	8·4	14·55	Needles,[2] 112—113°
,,	n-C_7H_{15}	H	91	—	—	—	$C_{14}H_{24}N_2O$	—	—	—	Waxy, indef. m. p.
Me	Me	Me	61	—	—	—	$C_7H_{10}N_2O$ *	—	—	—	178° ‡
Pr^i	,,	H	—	—	—	—	$C_8H_{12}N_2O$ §	—	—	—	Needles,[2] 172—173°
Bu^n	,,	,,	86	65·1	8·2	17·1	$C_9H_{14}N_2O$ ¶	65·05	8·5	16·85	Needles,[2] 120—121°
Me	Et	,,	68	59·9	7·6	—	$C_7H_{10}N_2O$	60·8	7·3	—	Needles,[5] 122—123°
,,	Pr^n	,,	57	64·2	8·0	18·8	$C_8H_{12}N_2O$	63·15	7·9	18·4	Leaflets,[3] 89—91°
,,	Bu^n	,,	—	64·1	8·3	16·8	$C_9H_{14}N_2O$	65·05	8·5	16·85	Needles,[6] 65—67°
Pr^n	Et	,,	76	64·8	8·3	16·9	$C_9H_{14}N_2O$	65·05	8·5	16·85	Needles,[4] 82—84°
,,	Me	Me	42	65·1	8·6	16·4	$C_9H_{14}N_2O$	65·05	8·5	16·85	Needles,[2] 132—133°
,,	,,	Et	38	66·3	8·9	15·7	$C_{10}H_{16}N_2O$	66·65	8·95	15·55	Needles,[4] 121—122°
,,	Cyclo-hexyl	H	—	70·9	9·3	12·6	$C_{13}H_{20}N_2O$	70·85	9·15	12·7	Plates,[7] 110—111°
Me	$-[CH_2]_4-$		75	66·4	7·5	16·7	$C_9H_{12}N_2O$ **	65·9	7·3	17·1	Needles,[8] 209—210°

* Ref. 11*a*. † Ref. 11*b*. ‡ Crude. § Ref. 11*c*. ¶ Yanai and Naito, *J. Pharm. Soc. Japan*, 1941, **61**, 99; *Chem. Abs.*, 1942, **36**, 479. ** McCasland and Bryce, *J. Amer. Chem. Soc.*, 1952, **74**, 842.

[1] From EtOH. [2] From EtOAc. [3] From EtOAc–light petroleum (b. p. 40—60°). [4] From H_2O. [5] From EtOAc; dried at 100°/vac. for analysis. [6] From light petroleum (b. p. 40—60°). [7] From light petroleum (b. p. 60—80°). [8] From Bu^nOH.

TABLE 3.

Hydrazinopyrimidines (VIII).

			Yield	Found (%)				Required (%)			M. p. or b.p./mm.,
R^1	R^2	R^3	(%)	C	H	N	Formula	C	H	N	etc.
Et	Me	H	68	55·5	7·9	37·0	$C_7H_{12}N_4$	55·25	7·95	36·8	Needles,[1] 148—150°
n-C_5H_{11}	,,	,,	95	61·5	9·8	28·2	$C_{10}H_{18}N_4$	61·8	9·35	28·85	68—70° [7]
Et	Et	,,	66	57·7	8·4	33·6	$C_8H_{14}N_4$	57·8	8·5	33·7	Needles,[3] 86—87°
,,	Pr^n	,,	64	60·4	9·0	—	$C_9H_{16}N_4$	59·95	8·95	—	187—189°/20
Pr^n	,,	,,	93	61·8	9·5	28·5	$C_{10}H_{18}N_4$	61·8	9·3	28·8	48—50° [9]
,,	Bu^n	,,	89	63·6	9·6	—	$C_{11}H_{20}N_4$	63·4	9·7	—	141—143°/0·4
,,	n-C_7H_{15}	,,	81	67·2	10·5	22·2	$C_{14}H_{26}N_4$	67·15	10·47	22·4	234—236°/24
Me	Me	Me	64	55·1	7·8	37·4	$C_7H_{12}N_4$	55·25	7·95	36·8	Plates,[10] 164—166°
Pr^n	,,	Pr^n	99	—	—	—	$C_{11}H_{20}N_4$	—	—	—	109—111°
,,	,,	Allyl	98	64·2	8·7	—	$C_{11}H_{18}N_4$	64·05	8·8	—	† [9]
Dipicrate			—	42·0	3·6	21·3	$C_{23}H_{24}N_{10}O_{14}$	42·5	3·7	21·1	Needles,‡ [1] 153—154°
H	Me	H	77	48·2	6·8	45·0	$C_5H_8N_4$ *	48·35	6·5	45·15	Needles,[11] 143—144°
Me	H	,,	—	49·7	7·0	—	$C_5H_8N_4$	48·35	6·5	—	Plates,[2] 122—124°
Pr^i	Me	,,	—	57·4	8·5	—	$C_8H_{14}N_4$	57·8	8·5	—	Needles,[7] 84—85°
Bu^n	,,	,,	71	59·5	8·9	30·8	$C_9H_{16}N_4$	59·95	8·95	31·1	Prisms,[7] 72°
Me	Et	,,	58	55·6	8·2	36·3	$C_7H_{12}N_4$	55·25	7·95	36·8	Prisms,[2] 127—128°
,,	Pr^n	,,	56	57·7	8·3	33·5	$C_8H_{14}N_4$	57·8	8·5	33·7	Needles,[2] 100—102°
,,	Bu^n	,,	95	60·0	8·8	—	$C_9H_{16}N_4$	59·95	8·95	—	Needles,[2] 83—85°
Pr^n	Et	,,	86	—	—	—	$C_9H_{16}N_4$	—	—	—	184—186°/25
,,	Me	Me	95	57·4	8·8	28·9	$C_9H_{16}N_4$ §	57·1	9·05	29·6	Needles,¶ [9] 78—80°
,,	,,	Et	95	59·4	9·4	27·5	$C_{10}H_{18}N_4$ §	59·05	9·4	27·5	Needles,‡ [9] 62—64°
,,	Cyclo-hexyl	H	99	—	—	—	—	—	—	—	—
Me	$-[CH_2]_4-$		85	61·0	7·9	31·1	$C_9H_{14}N_4$	60·65	7·9	31·4	Leaflets,[12] 178—180°

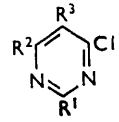
* Gabriel and Colman, *Ber.*, 1901, **34**, 1241; Shibo and Takahayashi, *J. Pharm. Soc. Japan*, 1955, **75**, 773. † Deliquescent solid. ‡ Yellow. § $+0·5H_2O$. ¶ Pale orange.

[1–3] See Table 1. [9] From Et_2O–light petroleum (b. p. 40—60°). [10] From CCl_4. [11] From chloroform. [12] From toluene.

[12] Yanai and Naito, *J. Pharm. Soc. Japan*, 1941, **61**, 99 (*Chem. Abs.*, 1942, **36**, 479).

TABLE 2.

6-Chloropyrimidines.



			Yield	Reaction	Found (%)					Required (%)				
R^1	R^2	R^3	(%)	time (hr.)	C	H	N	Cl	Formula	C	H	N	Cl	B. p./mm. or m. p.
Me	Me	H	—	—	—	—	—	—	*	—	—	—	—	—
Et	,,	,,	61	2·5	53·9	5·8	—	—	$C_7H_9N_2Cl$	53·8	5·75	—	—	93°/20
Bu^n	,,	,,	—	—	—	—	—	—	†	—	—	—	—	—
Bu^t	,,	,,	93	0·75	—	—	—	—	—	—	—	—	—	—
n-C_5H_{11}	,,	,,	54	4·0	60·9	7·5	14·1	—	$C_{10}H_{15}N_2Cl$	60·6	7·65	14·1	—	134—138°/25
Et	Et	,,	70	1·5	—	—	—	—	—	—	—	—	—	—
,,	Pr^n	,,	90	3·0	—	—	—	—	—	—	—	—	—	—
Pr^n	,,	,,	89	2·25	—	—	—	—	—	—	—	—	—	122—125°/18
,,	n-C_7H_{15}	,,	49	3·0	—	—	—	—	—	—	—	—	—	191—192°/26
,,	Me	Pr^n	75	3·0	62·2	8·0	—	—	$C_{11}H_{17}N_2Cl$	62·1	8·05	—	—	131—137°/10
,,	,,	Allyl	74	3·0	—	—	—	—	—	—	—	—	—	145—146°/30
,,	CF_3	H	96	0·5	—	—	—	—	—	—	—	—	—	—
Me	Me	Me	—	—	—	—	—	—	‡	—	—	—	—	—
H	,,	H	—	—	—	—	—	—	§	—	—	—	—	—
Me	H	,,	46	1·5	—	—	—	—	¶	—	—	—	—	Yellow needles, m. p. 55—57°
Pr^i	Me	,,	—	4·0	—	—	—	—	‖	—	—	—	—	—
Me	Et	,,	88	3·25	—	—	—	—	—	—	—	—	—	—
,,	Pr^n	,,	95	3·0	—	—	—	—	—	—	—	—	—	—
,,	Bu^n	,,	71	2·0	—	—	—	—	—	—	—	—	—	—
Pr^n	Et	,,	70	2·0	—	—	—	—	—	—	—	—	—	—
,,	Me	Me	64	3·0	—	—	—	—	—	—	—	—	—	122—126°/22
,,	,,	Et	62	3·0	—	—	—	—	—	—	—	—	—	130—132°/22
,,	Cyclohexyl	H	69	2·5	—	—	—	—	—	—	—	—	—	—
Me	–[CH_2]$_4$–		72	1·0	59·1	6·1	15·1	19·3	$C_9H_{11}N_2Cl$	59·15	6·0	15·35	19·45	132—133°/11 **

* Schmidt, *Ber.*, 1902, **35**, 1576. † Ref. ¶ of Table 1. ‡ Hull, Lovell, Openshaw, Payman, and Todd, *J.*, 1946, 357. § Gabriel and Colman, *Ber.*, 1899, **32**, 2931. ¶ Gabriel, *Ber.*, 1904, **37**, 3641. ‖ Margot and Gysin, *Helv. Chim. Acta*, 1957, **40**, 1569. ** Solidifies.

TABLE 4.

2-Amino-*s*-triazolo[2,3-*c*]pyrimidines (IX).

			Yield	Found (%)			Required (%)						
R^1	R^2	R^3	(%)	C	H	N	Formula	C	H	N	M. p., etc.	$\lambda_{max.}$ (mμ) (ε) ‡	$\nu_{max.}$ (cm.$^{-1}$)
Me	Me	H	70	51·3	5·9	43·1	$C_7H_9N_5$ *	51·5	5·55	42·9	Needles,[1] 250—252°	227 (44,000), *259* (4000)	3330s, 3180s, 1657s sh, 1651s, 1629vs, *1553*vs, 1528s, 1511ms sh
Et	,,	,,	74	54·7	6·5	39·3	$C_8H_{11}N_5$ *	54·2	6·25	39·5	Plates,[1] 196—197°	226 (39,700), *259* (4000), *297* (1700)	3330ms, 3140ms, 6128vs, *1551*vs, 1527s, 1502ms
n-C_5H_{11}	,,	,,	57	60·2	7·8	31·6	$C_{11}H_{17}N_5$ *	60·25	7·8	31·95	Plates,[2] 151—152°	230 (41,800), *260* (4300), *287* (2600)	3280s, 3130ms, 1641s, 1626vs, 1549vs, 1520ms, 1497ms
Et	Et	,,	63	56·7	6·8	36·6	$C_8H_{13}N_5$ *	56·5	6·85	36·6	Plates,[1] 159—160°	226 (39,300), *259* (4370), *296* (1600)	3280s, 3140ms, 1651vs, 1628vs, *1542*vs, 1526s, 1499s

TABLE 4. (*Continued.*)

R¹	R²	R³	Yield (%)	Found (%) C	H	N	Formula	Required (%) C	H	N	M.p., etc.	$\lambda_{max.}$ (mμ) (ε) ‡	$\nu_{max.}$ (cm.⁻¹)
Et	Pr^n	H	47	58·6	7·2	33·9	$C_{10}H_{15}N_5$ *	58·5	7·3	34·1	Plates,[1] 163—164°	229 (43,000), *258* (4100), *290* (1930)	3320s, 3160ms, 1640vs sh, 1628vs, *1550*vs, 1525s, 1501ms
Pr^n	,,	,,	56	60·1	7·8	32·5	$C_{11}H_{17}N_5$ *	60·25	7·8	31·9	Plates,[1] 158—159°	228 (32,350), *263* (3240), *290* (1600)	3280s, 3130ms, 1639vs, 1627vs, *1552*vs, 1520s, 1495ms
,,	Bu^n	,,	44	61·7	8·0	29·5	$C_{12}H_{19}N_5$ *	61·75	8·2	30·0	Plates,[1] 149—150°	222 (43,400), *253* (4200)	3340s, 3200ms, 1653vs, 1632vs, *1561*vs, 1529s, 1506ms
Pr^n	$C_7H_{15}^n$	,,	65	65·2	9	25·4	$C_{15}H_{25}N_5$ *	65·4	9·15	25·45	Plates,[1] 128—129°	230 (42,500), *262* (4700), *287* (2600)	3290ms, 3130, 1640s, 1622vs, *1550*vs, 1521ms, 1496ms
Me	Me	Me	87	54·1		39·2	$C_8H_{11}N_5$ *	54·2	6·25	39·5	Prisms,[1] 249—250°	228 (39,800), *258* (4900)	3290ms, 3180ms, 1648s, 1622vs, *1553*s, 1528vs, 1509s
Pr^n	,,	Pr^n	48	61·7	8·3	30·2	$C_{12}H_{19}N_5$ *†	61·75	8·2	30·0	Prisms,[1] 128—129°	232 (38,800), *266* (5240)	3300ms, 3260vs, 1608vs, *1549*s, 1520vs, 1504s sh
,,	,,	$CH_2{\cdot}CH{=}CH_2$ (Monohydrate)	62	58·0	7·6	28·2	$C_{12}H_{17}N_5$ *	57·8	7·7	28·1	Needles,[2] 86—87°	230 (31,400), *263* (3700)	3470ms, 3310ms, 3220s, 1651vs, 1620s, 1563s, 1531m, 1505ms
,,	CF_3	H	69	44·3	4·3	27·9	$C_9H_{10}F_3N_5$ *	44·1	4·1	28·55	Leaflets,[12] 148—149°	*208* (8600), 229 (32,200), *270* (3100), *303* (2400)	3340s, 3320ms sh, 3180ms 1643vs, *1561*s, 1538vs, 1508s
Me	H	,,	Low	48·1	4·8	—	$C_6H_7N_5$	48·3	4·75	—	Needles,[1] 228—230°	227 (36,000), *259* (3400), *284* (2000)	—
Pr^i	Me	,,	50	57·0	7·2	36·5	$C_9H_{13}N_5$	56·5	6·85	36·6	Needles,[1] 173—174°	228 (34,000), *260* (3900), *294* (3300)	—
Bu^n	,,	,,	48	58·3	7·4	34·4	$C_{10}H_{15}N_5$	58·5	7·35	34·1	Plates,[1] 169—170°	228 (40,000), *260* (3830), *294* (1440)	—
Me	Et	,,	82	54·4	6·3	39·6	$C_8H_{11}N_5$	54·2	6·25	39·5	Plates,[1] 198—200°	228 (44,050), *260* (4340), *295* (11,700)	—
,,	Pr^n	,,	65	56·7	6·7	36·8	$C_9H_{13}N_5$	56·5	6·85	36·6	Plates,[1] 182—184°	226 (38,200), *260* (3820), *297* (2220)	—
,,	Bu^n	,,	47	58·6	7·4	34·2	$C_{10}H_{15}N_5$	58·5	7·35	34·1	Plates,[1] 169°	229 (33,000), *259* (4120), *283* (1950)	—
Pr^n	Et	,,	55	58·7	7·3	34·0	$C_{10}H_{15}N_5$	58·5	7·35	34·1	Plates,[1] 152—153°	230 (45,500), *262* (4460), *286* (1845)	—
,,	Me	Me	33	58·6	7·2	34·4	$C_{10}H_{15}N_5$	58·5	7·35	34·15	Plates,[1] 148—149°	229 (40,000), *260* (5200)	—
,, (hemihydrate)	,,	Et	50	58·4	7·8	30·8	$C_{11}H_{17}N_5$, $0{\cdot}5H_2O$	57·9	7·95	30·7	Needles,[1] 115—116°	230 (42,100), *262* (5300)	—
,,	Cyclohexyl	H	—	64·8	8·3	27·1	$C_{14}H_{21}N_5$	64·8	8·15	27·0	Plates,[1] 120—122°	228 (41,600), *260* (5030)	—
Me	–[CH_2]$_4$– (hydrochloride)		64	50·2	5·8	28·7	$C_{10}H_{13}N_5$ ¶	50·1	5·85	29·2	Needles,[13] 298°	—	—

* Also prepared by the action of dilute hydrochloric acid on the corresponding [4,3-*c*] isomer. † Also prepared by reduction of the 8-allyl homologue in ethanol with hydrogen over platinum oxide. ‡ Italicised numerals denote inflexions in ultraviolet or shoulders in infrared spectra. §+0·5 H_2O. ¶ Hydrochloride; Found: Cl, 15·1. Reqd.: Cl, 14·8%. [1-2] See Table 1. [12] From light petroleum (b. p. 100—120°). [13] With decomp.; from aq. MeOH.

minimum quantity (600 ml.) of boiling water, and the solution was acidified to pH ~5 with concentrated hydrochloric acid. The suspension so obtained was cooled in ice–water. Filtration yielded the *hydroxypyrimidine* which crystallised from ethyl acetate as needles, m. p. 151—152°. Pinner [11c] gives m. p. 143° (from ethanol).

The *compounds* listed in Table 1 were prepared by the above method. Where the hydroxypyrimidine was appreciably soluble in water the acidified reaction mixture was evaporated to dryness and the residue was extracted with a suitable solvent, for example, ethyl acetate. All the compounds listed are colourless solids. The yields quoted, based on the amount of amidine hydrochloride used, are of practical-grade material, sufficiently pure for conversion into the chloropyrimidine.

4-*Hydroxy*-6-*methyl*-2-*t*-*butylpyrimidine*.—Ethyl acetoacetate (8·2 g.) was added gradually to a chilled solution of sodium (2·6 g.) in methanol (50 ml.), and to the resulting solution there was gradually added pivalamidine hydrochloride (7·0 g.). The mixture was cooled in ice–water for 2 hr., and then allowed to reach room temperature during 16 hr. Salt was removed by filtration and washed with methanol, and the combined methanolic filtrate and washings were evaporated to half-volume and diluted with water (*ca.* 75 ml.), treated with charcoal, and filtered. The filtrate was acidified with acetic acid, the suspension was cooled, and the solid was filtered off, washed with ice–water, and dried at 50°, to yield the *hydroxypyrimidine* (8·05 g.), m. p. 174—175°. Crystallisation from light petroleum (b. p. 100—120°) gave colourless needles of unchanged m. p. (Found: C, 65·1; H, 8·2; N, 17·1. $C_9H_{14}N_2O$ requires C, 65·0; H, 8·5; N, 16·85%).

4-*Hydroxy*-2-*n*-*propyl*-6-*trifluoromethylpyrimidine*.—A solution of ethyl trifluoroacetoacetate copper complex (8·1 g.) in methanol (40 ml.) was treated with hydrogen sulphide. The black precipitate was filtered off, and the filtrate was boiled to remove the excess of hydrogen sulphide. Butyramidine hydrochloride (5·0 g.) was then added to the solution, followed by sodium (2 g.) previously dissolved in methanol (33 ml.). Salt was removed and the filtrate was refluxed for 5 hr., acidified to pH 5 with acetic acid, and evaporated under reduced pressure. The residue was triturated with cold water (25 ml.) and cooled in ice–water, and the precipitate filtered off, washed with ice–water, and dried at about 60°, to yield the *hydroxypyrimidine* (5·7 g.), m. p. 81—82°. Crystallisation from light petroleum (b. p. 40—60°) gave cream-coloured needles, m. p. 83—84° (Found: C, 46·7; H, 4·3; N, 13·3. $C_8H_9F_3N_2O$ requires C, 46·7; H, 4·35; N, 13·6%).

4-*Hydroxy*-6-*methyl*-2,5-*di*-*n*-*propylpyrimidine*.—5-Allyl-4-hydroxy-6-methyl-2-propylpyrimidine (50 g.) in ethanol (250 ml.) was hydrogenated (10 atm.) in the presence of platinum oxide (0·5 g.) for 2 hr. Distillation of the filtered solution under reduced pressure gave the *hydroxypyrimidine* (42 g.), m. p. 95—96°, which crystallised from ethyl acetate (charcoal) in colourless needles, m. p. 101—102° (Found: C, 67·8; H, 9·1; N, 14·2. $C_{11}H_{18}N_2O$ requires C, 68·0; H, 9·3; N, 14·4%).

4-*Chloro*-6-*methyl*-2-*n*-*propylpyrimidine*.—4-Hydroxy-6-methyl-2-propylpyrimidine (263 g.) was added cautiously to phosphoryl chloride (650 ml.) which was stirred and cooled in a large volume of ice. The mixture was boiled under reflux for 3½ hr., concentrated to about one-third its volume under reduced pressure, cooled, poured on ice and water, and was kept alkaline by addition of 11N-sodium hydroxide. Extraction with chloroform followed by removal of the solvent and distillation at 95—100°/30 mm. gave the *chloropyrimidine* as a colourless liquid (Found: C, 56·3; H, 6·9; N, 16·1. $C_8H_{11}ClN_2$ requires C, 56·3; H, 6·5; N, 16·4%).

The *chloropyrimidines* listed in Table 2 were prepared in a similar manner. Only in comparatively few instances were the products distilled and analysed before conversion into the corresponding hydrazinopyrimidines.

4-*Hydrazino*-6-*methyl*-2-*n*-*propylpyrimidine*.—A solution of 4-chloro-6-methyl-2-propylpyrimidine (216 g.) in ethanol (350 ml.) was added dropwise to a boiling solution of hydrazine hydrate (140 ml., 2·2 equiv.) in ethanol (350 ml.). The mixture was boiled under reflux for 16 hr., then evaporated under reduced pressure. Extraction of the residue with warm chloroform and removal of the solvent under reduced pressure gave a solid (203 g.), m. p. 88—90°. Distillation gave a colourless liquid, b. p. 123—125°/0·65 mm., which solidified and on crystallisation from ethyl acetate gave the *hydrazinopyrimidine* as rectangular prisms, m. p. 93—95° (Found: C, 57·8; H, 8·4; N, 34·2. $C_8H_{14}N_4$ requires C, 57·8; H, 8·5; N, 33·7%), $\lambda_{max.}$ 203, 241, 263 infl. mμ (ε 9100, 10,400, 5000).

When less than 2·2 equiv. of hydrazine hydrate were used, a second, much less soluble

product, was obtained as colourless crystals (from ethyl acetate), m. p. 214—215° (Found: C, 63·6; H, 8·3; N, 27·6. $C_{16}H_{24}N_6$ requires C, 63·9; H, 8·05; N, 27·95%), $\lambda_{max.}$ 203, 228, and 273 mμ (ε 18,600, 14,250, and 11,250). This compound is probably NN′-*di*(6-*methyl*-2-*propylpyrimidin*-4-*ylhydrazine*).

Other *hydrazinopyrimidines* made by the method given above are listed in Table 3. The lower members of the series were readily purified by crystallisation, but for the higher members high-vacuum distillation was often preferable.

4-*Hydrazino*-2-*n*-*propyl*-6-*trifluoromethylpyrimidine*.—4-Chloro-2-propyl-6-trifluoromethylpyrimidine (4·8 g.) was added dropwise during 1 hr. to a solution of hydrazine hydrate (4·8 ml.) in ethanol (12 ml.) at 60°. The mixture was then refluxed for 2 hr., the solvent distilled off *in vacuo*, and the residue triturated with water. The solid was filtered off, washed with a little water, and air-dried, to yield the product (4·0 g.), m. p. 62—64°. This *product* crystallised as colourless rectangular prisms [from light petroleum (b. p. 80—100°)], m. p. 66—67° (Found: C, 43·5; H, 4·5; N, 25·5. $C_8H_{11}F_3N_4$ requires C, 43·65; H, 5·0; N, 25·45%).

4-*Hydrazino*-6-*methyl*-2-*t*-*butylpyrimidine*.—A solution of 4-chloro-6-methyl-2-t-butylpyrimidine (7·3 g.) in ethanol (15 ml.) was added dropwise during 40 min. to a stirred solution of hydrazine hydrate (6 ml.) in ethanol (20 ml.) at 60°. The mixture was then refluxed for 2 hr. and evaporated to dryness *in vacuo*. The residual oil solidified. It was ground with water (10 ml.), filtered off, washed with ice–water, and dried (6·2 g.; m. p. 67—69°). The *product* crystallised from light petroleum (b. p. 60—80°; carbon) as colourless needles, m. p. 72—73° (Found: C, 60·4; H, 8·8; N, 30·9. $C_9H_{16}N_4$ requires C, 59·95; H, 8·95; N, 31·1%).

4-*Hydrazino*-2,6-*dimethylpyrimidine*.[12]—4-Chloro-2,6-dimethylpyrimidine (20·5 g.) was added gradually during 5 min. to hydrazine hydrate (20 ml.) in water (20 ml.) at 50—60°. The mixture was then boiled for 5 min. and, after cooling to 0°, the precipitate was filtered off, washed with water at 0°, and dried at 60°, to yield the pale yellow *product* (15·2 g.), m. p. 186—187°. The same hydrazinopyrimidine was obtained in small yield by heating 4-amino-2,6-dimethylpyrimidine (2·5 g.) with hydrazine hydrate (5 ml.) for several days at 100°, under nitrogen.

3-*Amino*-s-*triazolo*[4,3-c]*pyrimidines*.

3-*Amino*-7-*methyl*-5-*n*-*propyl*-s-*triazolo*[4,3-c]*pyrimidine*.—4-Hydrazino-6-methyl-2-propylpyrimidine (5 g.) was dissolved in a mixture of water (50 ml.) and ethanol (15 ml.). Sodium carbonate (6 g.) was added and the solution was cooled to 10°. Passage of gaseous cyanogen chloride (2 g.) at 12—15° gave a yellow precipitate which was filtered off, washed with ice–water, and dried in a vacuum-desiccator over calcium chloride. The crude *triazolopyrimidine* (4·75 g.) was crystallised twice from a large volume of ethanol to yield colourless needles (1 g.), m. p. 238° (decomp.) [Found: C, 56·5; H, 6·9; N, 36·8%; *M* (ebulliosc. in magnesium-dried ethanol), 193. $C_9H_{13}N_5$ requires C, 56·5; H, 6·85; N, 36·6%; *M*, 191], $\lambda_{max.}$ 208, 264, and 316 mμ (ε 11,170, 7430, and 2530), $\nu_{max.}$ 3200ms sh, 3100s, 1652ms sh, 1628vs, 1582vs, 1564m sh, 1538m, and 1510ms cm.$^{-1}$.

Salicylaldehyde (0·2 ml.) was added to a solution of the above triazolopyrimidine (0·2 g.) in boiling ethanol (10 ml.) and the mixture was boiled under reflux for 18 hr. On cooling, the solution deposited yellow needles of the *salicylidene derivative*, m. p. 210—212° (Found: C, 65·2; H, 5·9. $C_{16}H_{17}N_5O$ requires C, 65·0; H, 5·8%), $\lambda_{max.}$ 212, 231, 278, and 371 mμ (ε 18,300, 10,400, 10,200, and 15,000), $\nu_{max.}$ 3050—2550ms, 1629vs, 1602s, 1574vs, 1551ms, and 1500 ms cm.$^{-1}$.

3-*Amino*-5,7-*dimethyl*-s-*triazolo*[4,3-c]*pyrimidine*.—A mixture of 4-hydrazino-2,6-dimethylpyrimidine (5 g.), water (50 ml.), ethanol (25 ml.), and sodium carbonate (6 g.) was treated with cyanogen chloride (2·4 g.) as above. The crude *triazolopyrimidine* (3·6 g.) was crystallised twice from ethanol, to yield colourless prisms, m. p. 270° (decomp.) (Found: C, 51·3; H, 6·2; N, 42·0. $C_7H_9N_5$ requires C, 51·5; H, 5·55; N, 42·9%), $\lambda_{max.}$ 206, 264, and 310 mμ (ε 10,700, 6400, and 2100), $\nu_{max.}$ 3230ms sh, 3130s, 1660s, 1630vs, 1587vs, 1541m, and 1513ms cm.$^{-1}$.

3-*Amino*-5-*ethyl*-7-*methyl*-s-*triazolo*[4,3-c]*pyrimidine*.—A mixture of 2-ethyl-4-hydrazino-6-methylpyrimidine (2·5 g.), water (25 ml.), ethanol (10 ml.), and sodium carbonate (2 g.) was treated with cyanogen chloride (1·1 g.) as above. The *triazolopyrimidine* (1·6 g.) crystallised from pyridine as colourless plates (0·6 g.), m. p. 237—238° (Found: C, 53·8; H, 5·8; N, 39·5. $C_8H_{11}N_5$ requires C, 54·2; H, 6·25; N, 39·5%), $\lambda_{max.}$ 207, 265, and 315 mμ (ε 12,100, 6870, and 2330), $\nu_{max.}$ 3250ms sh, 3130vs, 1660ms sh, 1650s sh, 1629vs, 1584vs, 1539, and 1511ms cm.$^{-1}$.

3-*Amino*-7-*methyl*-5-*t*-*butyl*-s-*triazolo*[4,3-c]*pyrimidine*.—4-Hydrazino-6-methyl-2-t-butylpyrimidine (5·4 g.) was dissolved in water (65 ml.) containing acetic acid (8 ml. of 5N) and sodium acetate (11 g.). The solution was kept at 0—2° while cyanogen chloride (2·0 g.) was passed in during 20 min. The suspension formed was cooled in ice–water for a further 10 min. and filtered. The yellow solid was washed with ice–water (3 × 5 ml.) and dried in a vacuum-desiccator over calcium chloride. This product (5·1 g.) sintered at 190° and melted at 193—195°. A portion (3 g.) was crystallised from xylene (30 ml.) by dissolution and cooling as rapidly as possible. The *triazolopyrimidine* was thus obtained as colourless plates (2·35 g.), m. p. 203—204° (Found: C, 58·1; H, 7·4; N, 34·1. $C_{10}H_{15}N_5$ requires C, 58·5; H, 7·3; N, 34·1%), $\lambda_{max.}$ 207, 261, and 315 mμ (ε 10,800, 5600, and 1700), $\nu_{max.}$ (KBr disc) 3280ms sh, 3160, 1638vs, 1568s, 1552ms sh, 1506m, (in $CHCl_3$) 3450mw, 3375m, 3280m, 3120m, 1638vs, 1620ms sh, 1564s, 1545ms sh, and 1508m cm.$^{-1}$.

When 3 equiv. of cyanogen chloride were used under the same conditions, a new *substance* was isolated as pale yellow leaflets, m. p. 126—127° (from butanol) (Found: C, 57·4; H, 5·8; N, 36·4. $C_{11}H_{14}N_6$ requires C, 57·3; H, 6·1; N, 36·5%).

3-*Amino*-7-*methyl*-5-*n*-*pentyl*-s-*triazolo*[4,3-c]*pyrimidine*.—4-Hydrazino-6-methyl-5-pentylpyrimidine (10 g.) in water (100 ml.), ethanol (50 ml.), and sodium carbonate (12 g.) was treated with cyanogen chloride (3·5 g.) at 12—15°. The yellow precipitate which formed was rapidly filtered off, washed with ice–water, and dried in a vacuum over calcium chloride. The *product* (7·5 g.) crystallised from chloroform (charcoal) as colourless plates, m. p. 219—220° (Found: C, 60·9; H, 8·1; N, 31·7. $C_{11}H_{17}N_5$ requires C, 60·25; H, 7·8; N, 31·95%), $\lambda_{max.}$ 207, 264, and 321 mμ (ε 10,200, 5600, and 1700), $\nu_{max.}$ 3220ms sh, 3110s, 1660ms sh, 1629vs, 1579vs, 1541m, 1508ms cm.$^{-1}$.

3-*Amino*-5,7-*diethyl*-s-*triazolo*[4,3-c]*pyrimidine*.—2,4-Diethyl-6-hydrazinopyrimidine (2·5 g.) in water (25 ml.), ethanol (5 ml.), and sodium carbonate (3 g.) was treated at 12—15° with cyanogen chloride (1 g.), and the colourless *product* was isolated as described above. This (2·1 g.), crystallised from chloroform, had m. p. 187° (Found: C, 56·9; H, 7·0. $C_9H_{13}N_5$ requires C, 56·5; H, 6·85%), $\lambda_{max.}$ 207, 263, and 313 mμ (ε 12,200, 6500, and 2000), $\nu_{max.}$ 3280ms, 3130s, 1661s, 1622vs, 1581vs, 1539m, and 1509ms cm.$^{-1}$.

3-*Amino*-5-*ethyl*-7-*n*-*propyl*-s-*triazolo*[4,3-c]*pyrimidine*.—Similarly 2-ethyl-4-hydrazino-6-propylpyrimidine (2·5 g.) in water (25 ml.), ethanol (10 ml.), and sodium carbonate (3 g.), on treatment with cyanogen chloride (0·9 g.) at 12—15°, gave a *product* (2 g.) that crystallised from ethanol as colourless plates, m. p. 222° (Found: C, 58·3; H, 7·5; N, 33·7. $C_{10}H_{15}N_5$ requires C, 58·5; H, 7·35; N, 34·1%), $\lambda_{max.}$ 206, 263, and 312 mμ (ε 12,300, 6600, and 2300), $\nu_{max.}$ 3210ms sh, 3100s, 1655ms sh, 1645ms sh, 1621vs, 1578vs, 1538m, and 1505m cm.$^{-1}$.

3-*Amino*-5,7-*di*-*n*-*propyl*-s-*triazolo*[4,3-c]*pyrimidine*.—Similarly prepared from 4-hydrazino-2,6-dipropylpyrimidine (5 g.) in water (50 ml.), ethanol (25 ml.), and sodium carbonate (6 g.), with cyanogen chloride (1·9 g.) at 12—15°, the crude *product* (5·2 g.) crystallised from chloroform (charcoal) as colourless plates, m. p. 216—217° (Found: C, 60·0; H, 7·9; N, 32·1. $C_{11}H_{17}N_5$ requires C, 60·25; H, 7·8; N, 31·95%), $\lambda_{max.}$ 202, 260, and 311 mμ (ε 12,000, 6900, and 2300), $\nu_{max.}$ 3210ms sh, 3120s, 1659ms sh, 1630vs, 1583vs, 1542m, and 1511ms cm.$^{-1}$.

3-*Amino*-7-*n*-*butyl*-5-*n*-*propyl*-s-*triazolo*[4,3-c]*pyrimidine*.—Similarly prepared from 4-butyl-6-hydrazino-2-propylpyrimidine (5 g.) in water (50 ml.), ethanol (30 ml.), and sodium carbonate (6 g.), with cyanogen chloride (1·7 g.) at 12—15°, this *product* (5·5 g.) crystallised from ethanol (charcoal) as needles, m. p. 220—221° (Found: C, 61·7; H, 8·3; N, 30·4. $C_{12}H_{19}N_5$ requires C, 61·75; H, 8·2; N, 30·0%), $\lambda_{max.}$ 209, 264, and 315 mμ (ε 10,930, 7050, and 2140), $\nu_{max.}$ 3180ms sh, 3110s, 1650ms sh, 1642ms sh, 1625vs, 1576vs, 1538m, 1505ms cm.$^{-1}$.

3-*Amino*-7-*n*-*heptyl*-5-*n*-*propyl*-s-*triazolo*[4,3-c]*pyrimidine*.—Similarly prepared from 4-heptyl-6-hydrazino-2-propylpyrimidine (2·5 g.) in water (25 ml.) and sodium carbonate (3 g.), with cyanogen chloride (0·7 g.) at 12—15°, this *product* formed colourless plates (0·35 g.) (from chloroform), m. p. 200° (Found: C, 65·3; H, 9·3; N, 25·4. $C_{15}H_{25}N_5$ requires C, 65·4; H, 9·15; N, 25·45%), $\lambda_{max.}$ 206, 262, and 313 mμ (ε 14,600, 7000, and 3000), $\nu_{max.}$ 3250ms sh, 3200ms sh, 3110s, 1655ms, 1627vs, 1578vs, 1536m, and 1508m cm.$^{-1}$.

3-*Amino*-5,7,8-*trimethyl*-s-*triazolo*[4,3-c]*pyrimidine*.—Similarly prepared from 4-hydrazino-2,5,6-trimethylpyrimidine (2·5 g.) in water (25 ml.), ethanol (15 ml.), and sodium carbonate (3 g.), with cyanogen chloride (1·4 g.) at 13—16°, this *product* formed colourless needles (1·5 g.) (from ethanol), m. p. 248—250° (decomp.) (Found: C, 54·2; H, 6·4; N, 39·5. $C_8H_{11}N_5$ requires C, 54·2; H, 6·25; N, 39·5%), $\lambda_{max.}$ 209, 264, and 315 mμ (ε 10,930, 7050, and 2140), $\nu_{max.}$ 3400m sh, 3300ms, 3130s, 1648s sh, 1627vs, 1585vs, 1563m sh, and 1514ms cm.$^{-1}$.

3-*Amino*-7-*methyl*-5,8-*di*-*n*-*propyl*-s-*triazolo*[4,3-c]*pyrimidine*.—Similarly prepared from 4-hydrazino-6-methyl-2,5-dipropylpyrimidine (5 g.) in water (20 ml.), sodium carbonate (5·4 g.), and ethanol (15 ml.), with cyanogen chloride (1·62 g.) at 10—15°, this *product* gave needles, m. p. 173—174°, after crystallisation twice from ethanol (Found: C, 61·4; H, 8·4; N, 29·8. $C_{12}H_{19}N_5$ requires C, 61·7; H, 8·2; N, 30·0%), $\lambda_{max.}$ 206, 267, and 312 mμ (ε 9400, 6100, and 2600), $\nu_{max.}$ 3300ms, 3090s, 1650ms sh, 1640ms sh, 1624vs, 1581ms, 1568ms, 1548ms, and 1510ms cm.$^{-1}$.

8-*Allyl*-3-*amino*-7-*methyl*-5-*n*-*propyl*-s-*triazolo*[4,3-c]*pyrimidine*.—Similarly prepared from 5-allyl-4-hydrazino-6-methyl-2-propylpyrimidine (10 g.) in water (50 ml.), sodium carbonate (9 g.), and ethanol (35 ml.), with cyanogen chloride (3·1 g.) at 10—15°, and crystallised from chloroform, this *product*, pale yellow (4·6 g.), had m. p. 170—172° (Found: C, 62·3; H, 7·3; N, 30·6. $C_{12}H_{17}N_5$ requires C, 62·3; H, 7·4; N, 30·3%), $\lambda_{max.}$ 207, 266, and 314 mμ (ε 11,250, 6600, and 2800), $\nu_{max.}$ 3300ms, 3090ms, 1654ms sh, 1638s sh, 1621vs, 1610ms sh, 1580ms, 1552ms, 1542ms, 1508ms cm.$^{-1}$.

3-*Amino*-5-*n*-*propyl*-7-*trifluoromethyl*-s-*triazolo*[4,3-c]*pyrimidine*.—Similarly prepared from 4-hydrazino-2-propyl-6-trifluoromethylpyrimidine (1·1 g.) in water (5·5 ml.), sodium carbonate (0·7 g.), and ethanol (5·5 ml.) with cyanogen chloride (0·35 g.) just below 10°, this *product* (0·85 g.; m. p. 183—184°) crystallised from ethyl acetate (charcoal) as cream rectangular prisms, m. p. 184° (Found: C, 44·5; H, 4·0; N, 29·0. $C_9H_{10}F_3N_5$ requires C, 44·1; H, 4·1; N, 28·55%), $\lambda_{max.}$ 219, 264, and 328 mμ (ε 10,400, 5060, and 2300), $\nu_{max.}$ 3420ms, 3280ms, 3080s, 1643vs, 1637s sh, 1582s, 1548ms, and 1520ms cm.$^{-1}$.

2-*Acetyl*-3-*imino*-7-*methyl*-5-*n*-*propyl*-s-*triazolo*[4,3-c]*pyrimidine* (XIV).—(*a*) Compound (VII) (1·5 g.), acetic anhydride (0·8 ml.), chloroform (30 ml.), and anhydrous sodium carbonate (1 g.) were shaken together for 1 hr. at room temperature, and then again after addition of water (10 ml.). The chloroform layer was dried (Na_2SO_4) and evaporated, to leave the *acetamide* which formed colourless crystals (from ethanol–water), m. p. 100—101° (Found: C, 57·1; H, 7·3; N, 29·7. $C_{11}H_{15}N_5O$ requires C, 56·7; H, 6·45; N, 30·05%), $\nu_{max.}$ 3290m, 2960m, 2870w, 1721vs, 1662s, 1630s, 1565s, and 1470m cm.$^{-1}$.

(*b*) 4-Hydrazino-6-methyl-2-propylpyrimidine was converted into its *acetyl derivative* by adding dilute aqueous ammonia to the solution obtained by shaking the base (2·1 g.) with water (10 ml.) and acetic anhydride (2 ml.). The product formed crystals (from ethyl acetate), m. p. 179—180° (Found: C, 58·1; H, 7·6; N, 26·4. $C_{10}H_{16}N_4O$ requires C, 57·7; H, 7·1; N, 26·9%). Cyanogen chloride (1·7 g.) was passed into a solution of the acetyl derivative (5·2 g.) in water (100 ml.) and 5N-sodium hydroxide (5 ml.) at 0—2°. The precipitate which was formed (3·75 g.) was extracted with cold benzene. Evaporation of the benzene left a solid which, successively crystallised from light petroleum (b. p. 40—60°), propanol, and methanol, gave colourless material, m. p. 102° undepressed with material from (*a*).

5,7-*Dialkyl*-2-*amino*-s-*triazolo*[2,3-c]*pyrimidines*.

2-*Amino*-7-*methyl*-5-*n*-*propyl*-s-*triazolo*[2,3-c]*pyrimidine* (X).—Cyanogen chloride (40·8 g., 1·1 equiv.) was bubbled during about ½ hr. into 4-hydrazino-6-methyl-2-propylpyrimidine (100 g., 1 equiv.) in N-hydrochloric acid (600 ml.) at 25—30°. The flask was stoppered, left at room temperature for 1 hr., and then partially evacuated to remove the excess of cyanogen chloride. Crystalline sodium acetate (*ca.* 300 g.) was added, and the cream-coloured precipitate was filtered off, washed with ice–water, dried at about 60°, and crystallised from ethanol (charcoal), to yield colourless needles of the *triazolopyrimidine*, m. p. 168—169°. A further recrystallisation from ethyl acetate yielded plates, m. p. 169·5—170° (Found: C, 56·6; H, 7·0; N, 36·4. $C_9H_{13}N_5$ requires C, 56·5; H, 6·85; N, 36·6%), $\lambda_{max.}$ 226, 259 infl., and 297 infl. mμ (ε 38,200, 4000, and 1700), $\nu_{max.}$ 3300s, 3160ms, 1650s, 1628vs, 1553vs, 1527s, and 1503 ms cm.$^{-1}$.

The *hydrochloride* was prepared by passing dry hydrogen chloride into a solution of the base (5 g.) in acetic acid (12·5 ml.) and dry ether (25 ml.) at 0°. The pale yellow precipitate was rapidly filtered off, washed with ether, dried at 60°, and crystallised from dry ethanol to give a colourless solid (2·4 g.), m. p. 213—215° (Found: C, 47·3; H, 6·0; N, 30·4; Cl, 15·4. $C_9H_{14}ClN_5$ requires C, 47·5; H, 6·2; N, 30·75; Cl, 15·55%). This compound was used for *X*-ray crystallographic studies.[9]

The *hydrobromide* was similarly prepared as pale cream crystals, m. p. 210—212°, from ethanol (Found: C, 39·7; H, 5·4; N, 25·6; Br, 29·8. $C_9H_{14}BrN_5$ requires C, 39·7; H, 5·2; N, 25·7; Br, 29·4%).

The *hydriodide* was prepared by addition of potassium iodide (2 g.) to a solution of the base (1·9 g.) in N-hydrochloric acid (10 ml.), and formed pale yellow crystals m. p. 206—208° (decomp.), from ethanol (Found: C 33·7; H, 4·5. $C_9H_{14}IN_5$ requires C, 33·85; H, 4·4%).

Table 4 lists further 2-amino-*s*-triazolo[2,3-*c*]pyrimidines made as in the preceding paragraphs.

2-*Amino*-7-*methyl*-s-*triazolo*[2,3-c]*pyrimidine*.—When 4-hydrazino-6-methylpyrimidine was treated with cyanogen chloride under standard acid conditions the only product isolated was ammonium chloride. The reaction was therefore studied in ethanol. Cyanogen chloride (1·4 g.) was passed into a solution of the hydrazinopyrimidine (2·5 g.) in ethanol (25 ml.) at 25—30°, and the flask was stoppered and left at room temperature for 1 hr. The precipitate was filtered off and washed with ethanol. The combined filtrate and washings were evaporated to dryness under reduced pressure at <30°. The residue was dissolved in water (10 ml.) and was treated with crystalline sodium acetate (5 g.) to give a pale yellow precipitate which was filtered off, washed with ice–water, and crystallised from ethanol, yielding the *triazolopyrimidine* as colourless needles (0·6 g.), m. p. 160° (Found: C, 47·9; H, 4·5; N, 46·8. $C_6H_7N_5$ requires C, 48·3; H, 4·7; N, 46·9%), $\lambda_{max.}$ 226, 261 infl., and 298 infl. mμ (ε 34,350, 2900, and 1900).

2-*Amino*-7-*methyl*-5-*t*-*butyl*-s-*triazolo*[2,3-c]*pyrimidine*.—A solution of 4-hydrazino-6-methyl-2-t-butylpyrimidine (1·8 g.) in water (10 ml.) containing 5N-hydrochloric acid (3 ml.) was treated with cyanogen chloride (0·7 g.) at <5°. After 1 hr., sodium acetate (3·5 g.) in water (8 ml.) was added, whereupon a semi-solid precipitate was formed. The bulk of the aqueous phase was removed by decantation. Acetic acid was added gradually to the residue until all the oily material had dissolved. The remaining solid was collected, washed with water, dried in air (0·5 g.; m. p. 184—186°), and crystallised from ethyl acetate (charcoal), to yield the *triazolopyrimidine* as colourless prisms, m. p. 186—187° (Found: C, 58·3; H, 7·3; N, 34·5. $C_{10}H_{15}N_5$ requires C, 58·5; H, 7·3; N, 34·1%), $\lambda_{max.}$ 225 and 263 mμ (ε 36,700 and 3100).

In a reaction at 25—30° the principal product was pivalamide, m. p. and mixed m. p. 152—153° (from methanol) (Found: C, 59·0; H, 10·9; N, 14·2. Calc. for $C_5H_{11}NO$: C, 59·4; H, 11·0; N, 13·85%). A small amount of the triazolopyrimidine was obtained from the mother-liquors.

2-*Amino*-7-*methyl*-5,8-*di*-*n*-*propyl*-s-*triazolo*[2,3-c]*pyrimidine*.—This was prepared by reduction of the monohydrate of the 8-allyl analogue in ethanol with hydrogen in the presence of platinum oxide.

2-*Amino*-8-(2,3-*dibromopropyl*)-7-*methyl*-5-*n*-*propyl*-s-*triazolo*[2,3-c]*pyrimidine*.—Bromine (1·2 ml.) was added gradually to a stirred solution of the corresponding 8-allyl derivative (5 g.; Table 4) in acetic acid (50 ml.) and water (25 ml.) at room temperature. The pale yellow solution was stirred at room temperature for a further few minutes and then cooled in ice–water. The precipitate was filtered off, washed with aqueous sodium acetate, then with ice–water, dried at 60°, and crystallised from ethanol, to yield colourless needles (2·0 g.) of the *bromo-derivative*, m. p. 145—146° (Found: C, 37·3; H, 4·4; N, 18·4. $C_{12}H_{17}Br_2N_5$ requires C, 36·9; H, 4·4; N, 17·9%), $\lambda_{max.}$ 234 and 269 mμ (ε 36,000 and 5590).

2-*Amino*-8-(2,3-*dihydroxypropyl*)-7-*methyl*-5-*n*-*propyl*-s-*triazolo*[2,3-c]*pyrimidine*.—Potassium permanganate (13·5 g.) in water (1350 ml.), was added to a solution of the corresponding 8-allyl derivative (12 g.; Table 4) in acetone (1·95 l.) at room temperature. After 1 hr. the mixture was filtered, neutralised with acetic acid, evaporated to small volume under reduced pressure, and cooled in ice–water. The precipitated *triazolopyrimidine* was filtered off, washed with ice–water, dried at 60°, and crystallised from ethanol as colourless needles (6·4 g.), m. p. 169—170° (Found: C, 54·6; H, 7·8; N, 26·1. $C_{12}H_{19}N_5O_2$ requires C, 54·3; H, 7·3; N, 26·4%), $\lambda_{max.}$ 232 and 268 mμ (ε 26,300 and 6180).

Action of Acid on 3-*Amino*-7-*methyl*-5-*t*-*butyl*-s-*triazolo*[4,3-c]*pyrimidine*.—(*a*) N-*Acetic acid*. The amine (100 mg.) was set aside in N-acetic acid (1 ml.) for 18·5 hr., then filtered off, washed with ice–water, and dried at about 60°; it was unchanged (m. p. and mixed m. p.).

(*b*) *Hydrochloric acid*. The amine (50 mg.) was dissolved in N-hydrochloric acid (1 ml.) and left at room temperature for 15 min. The solution was then treated with sodium acetate. The supernatant liquor was decanted from the sticky precipitate, which was washed with water by decantation and dissolved in ethanol. Slow addition of water and cooling gave colourless crystals, m. p. 184—186° alone or mixed with 2-amino-5-butyl-7-methyl-*s*-triazolo[2,3-*c*]-pyrimidine. The ultraviolet spectrum corresponded with that of the 2,3-*c* isomer.

(*c*) *Dilute hydrochloric acid* (*long storage*). The amine (0·7 g.) was dissolved in a solution of

concentrated hydrochloric acid (0·4 ml.) and water (2 ml.) and kept at room temperature. After 24 hr. the crystals which had been formed were filtered off, washed with a few drops of 2N-hydrochloric acid, and dried in air, to yield colourless prismatic needles of pivalamide, m. p. and mixed m. p. 151—152°. The aqueous mother-liquors were evaporated under reduced pressure below 50°, and the crystals which gradually appeared were triturated with acetone, filtered, and dried in air, to yield a colourless solid, beginning to melt at 75—77° but not completely molten until about 95° (Found: C, 30·5; H, 5·8; N, 29·2. $C_5H_8N_4O,HCl,H_2O$ requires C, 30·85; H, 5·65; N, 28·8%). This compound gave a strong diazo-reaction, and was thought to be 3-*acetonyl*-5-*amino*-s-*triazole hydrochloride monohydrate* (see below).

Various Treatments of 3-*Amino*-7-*methyl*-5-*n*-*propyl*-s-*triazolo*[4,3-c]*pyrimidine.*—(*a*) *Hydrochloric acid.* The base (191 mg.) was dissolved in 2N-hydrochloric acid (1·1 ml.) and left for 1 hr. at 22°. A very strong smell of butyric acid became apparent. Crystalline sodium acetate (1 g.) was added. The resulting suspension was cooled and filtered. The colourless solid obtained (80 mg.) had m. p. 168—169°, and showed no depression with the 2,3-*c* isomer. Addition of saturated aqueous picric acid to the filtrate gave a yellow precipitate which was filtered off, washed with ice–water, and dried (180 mg.); it had m. p. 188—189° alone or mixed with 3-acetonyl-5-amino-*s*-triazole picrate (see below). When the 2,3-*c* isomer was itself subjected to the same acid treatment, only a trace of butyric acid was detectable and addition of crystalline sodium acetate (1 g.) led to the almost quantitative recovery of the unchanged base.

(*b*) *Aqueous alkali.* The base (100 mg.) was heated in water (5 ml.) containing N-sodium hydroxide (1 ml.) for 15 min. on the steam-bath. The suspension was cooled and filtered to yield colourless plates (90 mg.), m. p. 168—170° alone or mixed with the 2,3-*c* isomer.

(*c*) *Boiling water.* The base (25 mg.) was heated under reflux in water (2·5 ml.) for 1 hr. Cooling and filtration yielded the 2,3-*c* isomer (20 mg.), m. p. and mixed m. p. 168—169°.

(*d*) *Dry heat.* The base (50 mg.) was heated in an open test-tube at 235° for 15 min., then cooled to room temperature and a small amount of crystalline sublimate (m. p. 166—168°, alone or mixed with the 2,3-*c* isomer) was removed. The brown oily residue crystallised from ethyl acetate (charcoal) to yield more (20 mg.) of the 2,3-*c* isomer, m. p. and mixed m. p. 168—169°.

(*e*) *Complete degradation.* The 2,3-*c* isomer base (22·8 g.) was boiled under reflux for 1·5 hr. with N-hydrochloric acid (360 ml.) (strong smell of butyric acid), then evaporated to dryness azeotropically with ethanol and benzene under reduced pressure. The residue was extracted with cold ethanol (50 ml.); the solid (mostly ammonium chloride) was washed with more cold ethanol (10 ml.). The combined filtrates were diluted with dry ether until cloudy and then kept at 0° overnight. The granular precipitate (10·5 g.; m. p. 76—77°) gave no depression of the m. p. with the material from 3-amino-7-methyl-5-t-butyl-*s*-triazolo[4,3-*c*]-pyrimidine (see above) and is probably 3-acetonyl-5-amino-*s*-triazole hydrochloride hydrate. Recrystallisation (1 g.) from ethanol–ether gave a colourless *semihydrate* (0·5 g.), m. p. 141—143° (Found: C, 32·4; H, 5·6. $C_5H_8N_4O,HCl,0·5H_2O$ requires C, 32·4; H, 5·4%).

A portion (1 g.) of the monohydrate in water was treated with sodium hydrogen carbonate until effervescence ceased. The solution was evaporated under reduced pressure azeotropically with ethanol and benzene, and the residue was extracted with boiling ethanol. Concentration of the extract, and chilling, gave 3-*acetonyl*-5-*amino*-s-*triazole*, m. p. 121—122° (Found: C, 42·3; H, 5·9; N, 39·3. $C_5H_8N_4O$ requires C, 42·85; H, 5·75; N, 40·0%), giving no ultraviolet peaks above 205 mμ and $\nu_{max.}$ 1708vs, 1652s, 1642s, 1601ms, and 1539ms cm.$^{-1}$. The anhydrous base and the original hydrated hydrochloride afforded a *picrate*, yellow needles (from ethanol), m. p. 188—189° (Found: C, 36·0; H, 3·0; N, 26·3. $C_{11}H_{11}N_7O_8$ requires C, 35·8; H, 2·9; N, 26·55%).

The hydrated hydrochloride and *p*-nitrophenylhydrazine in boiling ethanol containing acetic acid gave the p-*nitrophenylhydrazone* as orange needles (from ethanol), m. p. 140° (decomp.) (Found: C, 47·8; H, 5·0; N, 35·3. $C_{11}H_{13}N_7O_2$ requires C, 48·0; H, 4·7; N, N, 35·6%), $\lambda_{max.}$ 205, 249, and 390 mμ (ε 14,000, 8600, and 19,600) [cf. acetone *p*-nitrophenylhydrazone, $\lambda_{max.}$ 203, 249, and 394 mμ (ε 10,000, 8100, and 19,200); the infrared spectra also closely resembled one another].

3-Amino-5-ethyl-7-methyl-*s*-triazolo[4,3-*c*]pyrimidine (171 mg.), when similarly treated, gave a colourless solid (100 mg.), m. p. 196—197° alone or mixed with 2-amino-5-ethyl-7-methyl-*s*-triazolo[2,3-*c*]pyrimidine. Addition of picric acid to the mother-liquors gave yellow needles (110 mg.), m. p. 188—189° alone or mixed with 3-acetonyl-5-amino-*s*-triazole picrate.

The compounds shown on Table 4 marked * were prepared from the appropriate 3-amino-*s*-triazolo[4,3-*c*]pyrimidine and N-hydrochloric acid (10—25 parts by wt.) at room temperature (~15 min.). The products were isolated by addition of an excess of sodium acetate to the chilled acid solution. In all cases the products had the same m. p.s (no depression of mixed m. p.s) as the corresponding compounds made directly from the corresponding hydrazinopyrimidine in dilute hydrochloric acid with cyanogen chloride.

2-*Amino*-7-*methyl*-5-*n*-*propyl*-s-*triazolo*[2,3-c]*pyrimidine Methobromide*.—Dimethyl sulphate (0·7 ml.; neutralised with sodium carbonate immediately before use) was added to a solution of the triazolo[2,3-*c*]pyrimidine (0·95 g.) in nitrobenzene (3 ml.) at 140°. The mixture was heated at 130—140° for 2 min., cooled, and diluted with acetone (10 ml.). The precipitate was filtered off, washed with acetone, and dried (0·75 g.). Most (0·65 g.) of the solid was dissolved in water (3 ml.), to which sodium bromide (1·0 g.) was then added. The mixture was warmed to effect complete dissolution, then chilled. The *methobromide* was filtered off, and crystallised from water as pale yellow needles (0·15 g.), m. p. 265° (decomp.) (Found: C, 41·0; H, 5·3; N, 23·5; Br, 28·9. $C_{10}H_{16}BrN_5$ requires C, 41·9; H, 5·6; N, 24·5; Br, 28·0%), $\lambda_{max.}$ 226 and 267 mμ (ε 18,620 and 8490).

The *methiodide* was similarly prepared by using sodium iodide. It formed pale yellow crystals (from butan-1-ol), m. p. 258—259° (decomp.) (Found: C, 36·4; H, 5·1: N, 20·6; I, 37·6. $C_{10}H_{16}IN_5$ requires C, 36·05; H, 4·85; N, 21·0; I, 38·1%), $\lambda_{max.}$ 222 and 267 mμ (ε 49,900 and 8900).

11N-Sodium hydroxide (5 ml.) was added to a solution of the methiodide (5 g.) in boiling water (50 ml.), and the mixture was then cooled in ice–water. The resulting precipitate was filtered off, crystallised from boiling water, washed with ice–water, and dried at about 60° to yield a *substance* (?XVII or XVIII) as colourless leaflets (1·4 g.), m. p. 196° (decomp.) (Found: C, 53·9; H, 7·4; N, 31·0. $C_{10}H_{17}N_5O$ requires C, 53·8; H, 7·6; N, 31·4%), $\lambda_{max.}$ 208, 235, and 298 mμ (ε 5200, 6200, and 14,500).

This substance (1·5 g.) was boiled with N-hydrochloric acid (20 ml.) for 1·5 hr., and the solution was evaporated to dryness azeotropically with ethanol and benzene. The distillate had a strong smell of butyric acid. The residue was extracted with ethanol, and the extract was diluted with ether and cooled in ice–water. Colourless crystals separated slowly, which recrystallised as needles (0·4 g.), m. p. 78—79° (Found: C, 34·2; H, 6·8; N, 26·7; Cl, 17·4. $C_6H_{10}N_4O,HCl,H_2O$ requires C, 34·5; H, 6·3; N, 26·8; Cl, 17·0%), $\nu_{max.}$ 1740 sh, 1702, and 1681 cm.$^{-1}$ (no ultraviolet peak above 200 mμ), giving a positive nitroprusside reaction for $CO{\cdot}CH_2$. It was probably an *N*-methylated 3-acetonyl-5-amino-*s*-triazole.

Acyl (*etc.*) *Derivatives of* 2-*Amino*-7-*methyl*-5-*n*-*propyl*-s-*triazolo*[2,3-c]*pyrimidine* (X).—(*a*) The base (159 g.), acetic acid (400 ml.), and acetic anhydride (160 ml.) were boiled under reflux for 30 min., then cooled in ice–water until no more solid separated. The precipitate crystallised from ethanol to yield the *acetyl derivative* (XI) as needles (162·5 g.), m. p. 174° (Found: C, 56·8; H, 6·5; N, 30·0. $C_{11}H_{15}N_5O$ requires C, 56·65; H, 6·5; N, 30·05%), $\lambda_{max.}$ 227 and 257 infl. mμ (ε 44,500 and 5200), $\nu_{max.}$ 3200m sh, 1120m, 1167m, 1203ms, 1321vs, 1374ms, 1418m, 1428m, 1517s, 1542vs, 1565vs, 1632s, 1692s, and 1699s sh cm.$^{-1}$. A *sodium salt* separated when the acetyl derivative (1 g.) in warm ethanol (5 ml.) containing sodium hydroxide (0·174 g.) was cooled at 0°. It formed a white solid, m. p. 236—238° (decomp.), from ethanol (Found: C, 52·1; H, 5·9. $C_{11}H_{14}N_5NaO$ requires C, 51·8; H, 5·5%).

A *methyl derivative* was precipitated when dimethyl sulphate (1·4 ml.) was added gradually to a solution of the acetamido-compound (1·75 g.) in aqueous 2N-sodium hydroxide (22·5 ml.), stirred at room temperature. It formed colourless needles (0·25 g.), m. p. 117—119° (from ethyl acetate) (Found: C, 58·8; H, 7·3; N, 34·7. $C_{10}H_{15}N_5$ requires C, 58·5; H, 7·4; N, 34·1), $\lambda_{max.}$ 235, 264 infl., and 298 mμ (ε 47,200, 7720, and 2580), and is probably 7-methyl-2-methylamino-5-propyl-*s*-triazolo[2,3-*c*]pyrimidine.

(*b*) The base (1·9 g.), pyridine (5 ml.), and stearoyl chloride (3·75 g.) were boiled under reflux for 3 hr., cooled, and added to ice. The *stearamide* was filtered off, washed with water, dried, and crystallised from ethyl acetate (charcoal) as needles (2·6 g.), m. p. 90—92° (Found: C, 70·5; H, 10·1; N, 15·9. $C_{27}H_{47}N_5O$ requires C, 70·85; H, 10·35; N, 15·3%), $\lambda_{max.}$ 228 and 251 infl. mμ (ε 50,000 and 8000), $\nu_{max.}$ 3230mw, 3130m, 1686s, 1634s, 1552vs, and 1519s cm.$^{-1}$. The nuclear magnetic resonance spectrum was measured by Dr. J. K. Becconsall of Imperial Chemical Industries Limited, Dyestuffs Division, Hexagon House, Manchester, using a Varian V-4300B spectrometer operating at 40 Mc./sec. A peak at τ −0·65 p.p.m. (chloroform peak,

τ 2·75, as reference) was considered to be due to the NH·CO proton, in fair agreement with that for similar protons.

(*c*) The base (6 g.) in 98% formic acid (31·4 ml.) was boiled for 1 hr. and then evaporated under reduced pressure. The residue was crystallised twice from ethanol to yield the *formamide* as plates (2·75 g.), m. p. 189—190° (Found: C, 54·9; H, 6·2; N, 31·9. $C_{10}H_{13}N_5O$ requires C, 54·8; H, 6·0; N, 31·95%), $\lambda_{max.}$ 228 and 256 infl. mμ (ε 39,000 and 5300).

(*d*) The base (5 g.), maleic anhydride (2·55 g.), and dioxan (50 ml.) were boiled under reflux for 2 hr., then evaporated under reduced pressure. The residue was triturated with ethyl acetate, and the precipitate was crystallised from ethanol–ethyl acetate to yield the β-*carboxyacrylamide*, m. p. 170—171°, readily soluble in aqueous sodium hydrogen carbonate (Found: C, 53·5; H, 5·2; N, 23·8. $C_{13}H_{15}N_5O_3$ requires C, 53·95; H, 5·25; N, 24·2%), $\lambda_{max.}$ 220 and 248 infl. mμ (ε 26,400 and 14,500).

A solution of this maleamic acid (2 g.) in dimethylformamide (30 ml.) was shaken with hydrogen in the presence of platinum oxide (0·1 g.) (150 ml. absorbed; N.T.P.). A precipitate was formed which was filtered off and crystallised twice from ethanol, to yield the β-*carboxypropionamide* (0·5 g.), m. p. 204—206° (Found: C, 53·2; H, 6·2; N, 24·1. $C_{13}H_{17}N_5O_3$ requires C, 53·6; H, 5·9; N, 24·05%).

(*e*) The base (5 g.), phthalic anhydride (5 g.), and acetic acid (25 ml.) were boiled under reflux for 2 hr., then cooled to room temperature. The precipitate formed on addition of water and cooling was filtered off, washed with ice–water, dried at 60°, and crystallised from ethanol to yield the *phthalimide* as rectangular plates (2·9 g.), m. p. 175—176° (Found: C, 63·3; H, 4·6; N, 21·7. $C_{17}H_{15}N_5O_2$ requires C, 63·55; H, 4·7; N, 21·8%), $\lambda_{max.}$ 225 mμ (ε 57,000).

(*f*) The base (5 g.), salicylaldehyde (5 g.), and ethanol (50 ml.) were heated under reflux for 15·5 hr. and then cooled. The precipitate was collected and crystallised twice from ethanol, to yield the *salicylidenederivative* as yellow needles (3·15 g.), m. p. 141—142° (Found: C, 65·0; H, 5·6; N, 23·6. $C_{16}H_{17}N_5O$ requires C, 65·05; H, 5·8; N, 23·7%), $\lambda_{max.}$ 222, 269, 288, and 354 mμ (ε 25,400, 16,430, 15,580, and 8220), readily soluble in aqueous sodium hydroxide to give a bright yellow solution.

This derivative (1 g.), dissolved in ethanol (100 ml.) and dimethylformamide (10 ml.), was reduced with hydrogen (140 ml. at N.T.P.) in the presence of platinum oxide (0·1 g.). The catalyst was filtered off, the almost colourless solution was evaporated under reduced pressure, and the residue crystallised from ethyl acetate–light petroleum (b. p. 60—80°) to yield the 2-o-*hydroxybenzylamino-derivative* as colourless prisms, m. p. 145—146° (Found: C, 64·3; H, 6·2; N, 23·4. $C_{16}H_{19}N_5O$ requires C, 64·6; H, 6·45; N, 23·55%), $\lambda_{max.}$ 204, 234, 271, and 296 mμ (ε 11,600, 44,400, 5800, and 2900).

(*g*) Chloral (1·5 g.) was boiled with the base (1·9 g.) in dry dioxan (20 ml.) for 30 min. The syrup which remained after removal of the solvent was triturated with ether–light petroleum (b. p. 60°) to yield the colourless 2-(2,2,2-*trichloro*-1-*hydroxyethylamino*)-*derivative* (2·7 g.), m. p. 122—123° (unchanged on crystallisation from the same mixture) (Found: C, 39·2; H, 4·1; N, 20·9; Cl, 30·6. $C_{11}H_{14}Cl_3N_5O$ requires C, 39·0; H, 4·15; N, 20·7; Cl, 31·4%), $\lambda_{max.}$ 229 and 256 infl. mμ (ε 47,000 and 4600).

(*h*) A mixture of benzoyl chloride (3·8 ml.) and the base (5 g.) in dry pyridine (25 ml.) were heated on a steam-bath for 2 hr., then cooled and stirred into ice–water. The off-white precipitate was collected, washed with water, and crystallised from ethanol, to yield the colourless *benzamide* (6 g.), m. p. 148—149° (Found: C, 65·0; H, 5·8; N, 23·1. $C_{16}H_{17}N_5O$ requires C, 65·05; H, 5·8; N, 23·7), $\lambda_{max.}$ 241 mμ (ε 26,000).

(*i*) Toluene-*p*-sulphonyl chloride (2·1 g.) and the base (1·9 g.) in dry pyridine (8 ml.) were heated on a steam-bath for 2 hr. and worked up as described above. The *sulphonamide* formed colourless crystals (1 g.) (from ethanol), m. p. 206—207° (Found: C, 55·1; H, 5·0; N, 20·1; S, 9·3. $C_{16}H_{19}N_5O_2S$ requires C, 55·65; H, 5·55; N, 20·3; S, 9·3%), $\lambda_{max.}$ 220 and 254 infl. mμ (ε 35,000 and 7100).

The authors thank Dr. J. M. Pryce for determination and interpretation of spectra, and Messrs. W. Broadbent and D. G. Smith for technical assistance.

Imperial Chemical Industries Limited, Pharmaceuticals Division,
Alderley Park, Macclesfield, Cheshire. [*Received, April 19th*, 1963.]