Allenes. Part 50.[1] Pyrimido[1,2-*a*]pyrimidines and Pyrimido[1,6-*a*]pyrimidines and their Hydrolysis Products from Allenic Nitriles and Phenylpropynenitrile

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2-Aminopyrimidine and 2-amino-4-methylpyrimidine react with allenic nitriles to give, initially, 2-imino-4-alkylpyrimido[1,2-*a*]pyrimidines (**2**) which rapidly add water and cleave to 3-(4-amino-6-alkyl-2-pyrimidylamino)aldehydes (**6**). 2-Amino-4,6-dimethylpyrimidine similarly gives the corresponding ketones (**5**; $R^3 = R^4 = Me$). 2-Imino-4-alkylpyrimido[1,6-*a*]pyrimidines (**11**) are formed as intermediates from 4-amino-2,6-dimethylpyrimidine and allenic nitriles and are hydrolysed to amides (**12**).

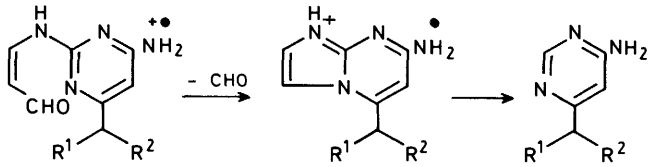
We have recently synthesised pyrido[1,2-*a*]pyrimidines[2] from allenic nitriles and have shown that such heterocycles hydrolyse spontaneously under mild basic conditions. We now report that pyrimido[1,2-*a*]pyrimidines are formed similarly from allenic nitriles and 2-amino- and 4-amino-pyrimidines but are spontaneously hydrolysed by a completely different route. Pyrimido[1,2-*a*]pyrimidines have been shown to be of potential pharmaceutical importance.[3]

2-Aminopyrimidine (**1a**) heated under reflux with allenic nitriles in ethanol gives hydrolysis products of pyrimido[1,2-*a*]-pyrimidines which show a carbonyl carbon in the ^{13}C n.m.r. spectrum at 197. However, the mass and ^1H n.m.r. spectra exclude the enaminic ketone structure (**7a**) which would result from the addition of water in the 4-position, as they neither eliminate the alkyl side chain ($-CHR^1R^2$) on fission nor show the chelated NH ··· O=C at δ_H 14 in the ^1H n.m.r. spectrum, typical of such compounds.[2] Instead a doublet is found at δ_H 9.315 which is assigned to an aldehyde proton, O=C*H*–CH= and, in all cases, the molecular ion M^+ loses CHO (**29**) to give the base peak.

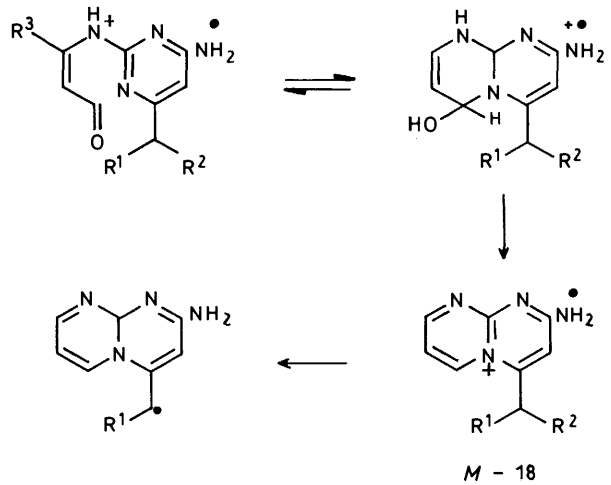
There is only one aldehyde which can be obtained from the hydrolysis of the pyrimido[1,2-*a*]pyrimidine (**2**; $R^4 = H$), which must result from attack by a water molecule at the C-6 position. Pyrimidopyrimidines contain two pyrimidine rings which may be attacked by a nucleophile at one of the positive centres, either at C-4 or C-6 next to the positive nitrogen [shown in resonance form (**3**)]. Conclusive evidence presented here shows that they are always attacked at C-6 (unlike the pyrido[1,2-*a*]pyrimidines[2] which have only one pyrimidine ring and are therefore always attacked at C-4) and if C-6 is unsubstituted an aldehyde is always obtained. Starting with 2-amino-4-methylpyrimidine, the ring nitrogen furthest from the methyl adds to the central carbon of the allene (electronically more favourable and to minimise steric interaction) and the resulting pyrimidopyrimidine (**2**) has $R^3 =$ Me, $R^4 = H$ which on hydrolysis again gives an aldehyde.

Detailed examination of high-field proton, carbon, and mass spectra shows that *E* and *Z*, (**6**) ⇌ (**5**), and ring–chain tautomeric forms, (**5**) ⇌ (**4**), are often encountered (see Table), although the proportions vary considerably according to the substituents present and the experimental conditions. Where $R^3 = R^4 = H$ the *E* form (**6**) predominates with the coupling constant of H^1 and H^2 of the aldehyde side chain $J = 8$—10 Hz. Where $R^3 =$ Me, $R^4 = H$ the product is almost entirely in the *Z* form (**5**); the coupling constant for H^1 and H^2 $J = 3$—4 Hz, with the strongly hydrogen bonded NH ··· O=C signal being at δ 12—13.

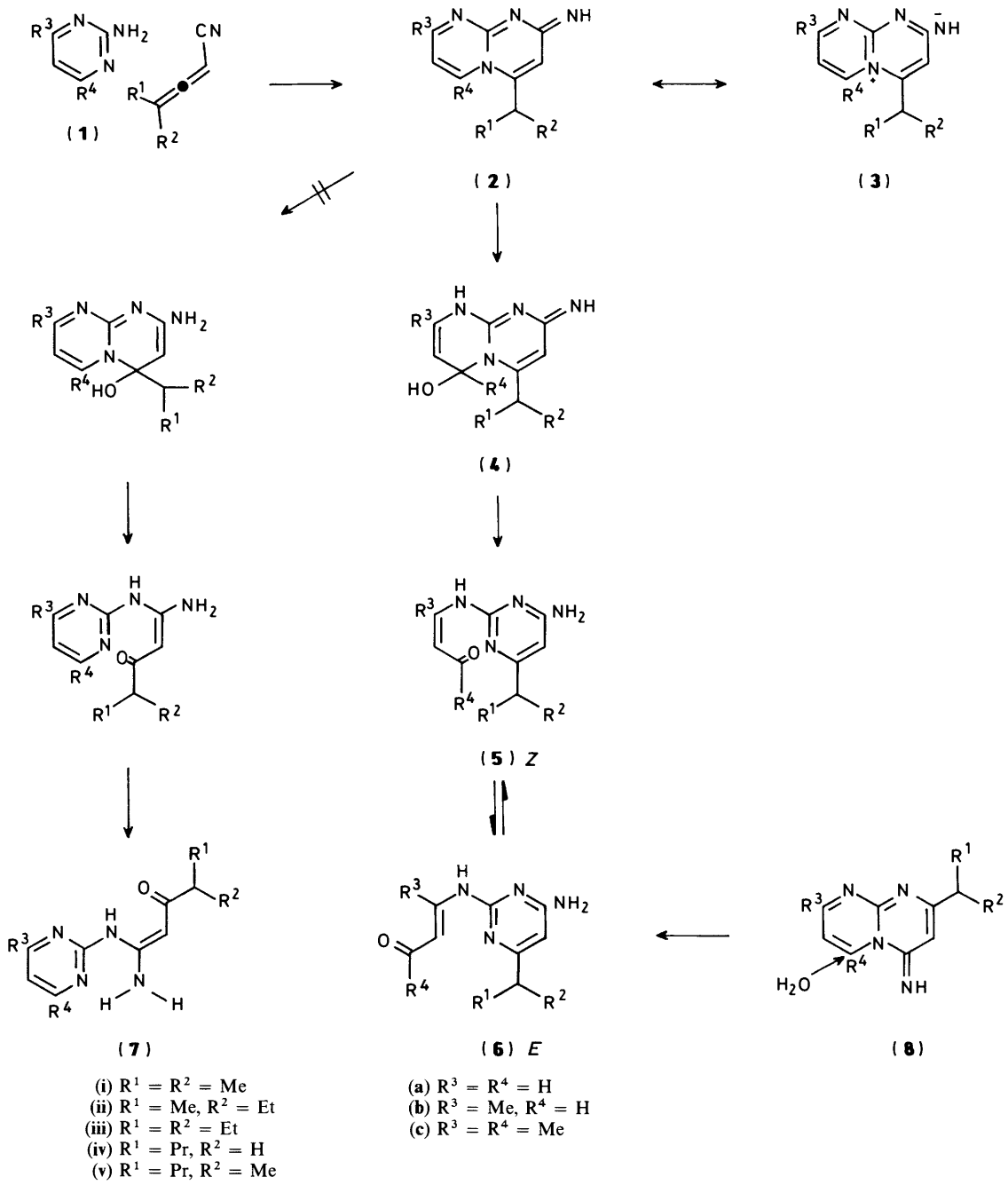
In their mass spectrum all the aldehydes give a base peak of $M - 29$ for loss of CHO and form the stable imidazolopyrimidine radical cation (**9**). This is usually cleaved further by loss of C_2H_2N or C_2H_3N (azirine) to give the 4-amino-6-alkylpyrimidine fragment (**10**). However, in addition to this



principal mode of fission, substantial peaks for $M - 18$ are observed and these fragments are usually further degraded by loss of alkyl from the side chain on C-4, either by McLafferty rearrangement or alkyl radical fission. This supports a ring–chain equilibrium and, under mass spectral conditions, a reversal of the hydrolysis.



It should be noted that the same structure (**5**) and (**6**) would also result from the hydrolysis of the alternative 4-imino-2-alkylpyrimidopyrimidine (**8**), but in the absence of any evidence to the contrary and in view of the conclusive evidence of the



Scheme 1.

structure of 2-iminopyridopyrimidines,[2] the 4-alkyl-2-imino-pyrimido[1,2-*a*]pyrimidine pathway is preferred.

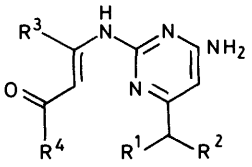
With an alkyl group in the 6-position hydrolysis either by attack at C-4 or C-6 must form a ketone. However, attack again takes place at the 6-position as shown by the following spectroscopic data which confirm the structure as ketone (**5**) in the *Z* form. Both ^{13}C and ^{1}H n.m.r. signals for the ketone side chain show constant values regardless of R^1 and R^2. A signal at δ_C 197.2 shows a ketone carbonyl (C-3′) while the methyl on C-1′ resonates at δ_C 22.95 and the 4′-methyl at δ_C 29.76. The alternative scheme which shows water attacking at C-4 of the pyrimidopyrimidine (**2**) giving (**7c**) (in which the 4- and 6-methyls are equivalent) can therefore be rejected.

The ^{1}H n.m.r. signal at δ_H 12.37 (for NH · · · O=C) shows that the ketones are entirely in the *Z* form*; a doublet at δ 2.51 (*J* 0.4 Hz) for the methyl on C-1′ (long-range coupling with proton on C-2′) and a singlet at δ 2.101 for the 4′-methyl fit structure (**5**) but not (**7c**), as do a doublet for the proton on C-2′ at δ 5.93—5.95 (*J* 0.3 Hz) and a singlet for the proton at C-5 of the pyrimidine ring at δ 5.196. The molecular ion in each case loses $CH_3C{\equiv}O$ to give the stable imidazopyrimidine as the base peak at *M* − 43, with a small *M* − 15 peak for the alternative loss of Me from the acetyl.

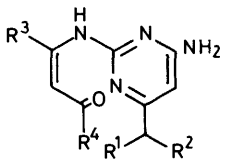
A number of attempts were made to convert 2-amino-pyrimidine hydrochloride into 2-amino-4-alkylpyrimido[1,2-

* For (**7c**) the chelated NH signal would be expected near δ_H 14.

Table. Preparation of condensation products



(6)



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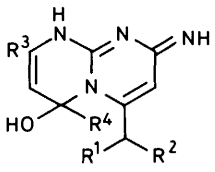
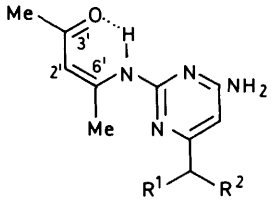


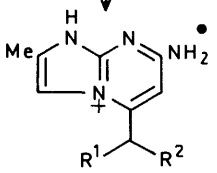
(4)

Entry	R^1	R^2	R^3	R^4	Time (h)	Yield (%)	M.p. (°C)	Found C	Found H	Found N	Required C	Required H	Required N	(6):(5):(4)
1	Me	Me	H	H	72	41[a]	160	57.9	6.7	26.8	58.3	6.8	27.2	14:1:1
2	Me	Et	H	H	78	43[a]	175	59.8	7.4	25.2	60.0	7.27	25.5	14:1:2
3	Et	Et	H	H	78	42[a]	173	61.5	7.4	23.7	61.5	7.69	23.9	*b*
4	H	Pr	H	H	120	68	140	59.9	7.2	25.2	60.0	7.27	25.5	2:3:2
5	Et	Et	Me	H	72	42[a]	115	62.7	7.8	22.6	62.9	8.06	22.6	0:1:0
6	Me	Me	Me	Me	48	41[a]	136	61.5	7.7	24.0	61.5	7.69	23.9	0:1:0
7	Me	Et	Me	Me	48	40[a]	150	62.9	8.1	22.7	62.9	8.06	22.6	0:1:0
8	Et	Et	Me	Me	48	64	121	64.0	8.4	21.5	64.1	8.40	21.4	0:1:0
9	Me	Pr	Me	Me	48	50	129	64.1	8.4	21.5	64.1	8.40	21.4	*b*
10	Ph[c]		H	H	60	56	210	65.1	4.9	23.4	65.0	5.00	23.3	*b*

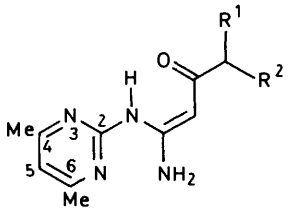
[a] *ca.* 40% of starting pyrimidine was recovered. [b] High-field ^1H and ^{13}C n.m.r. signals not determined. [c] R^1R^2CH=Ph.



(5c)



M − 43 (100%)

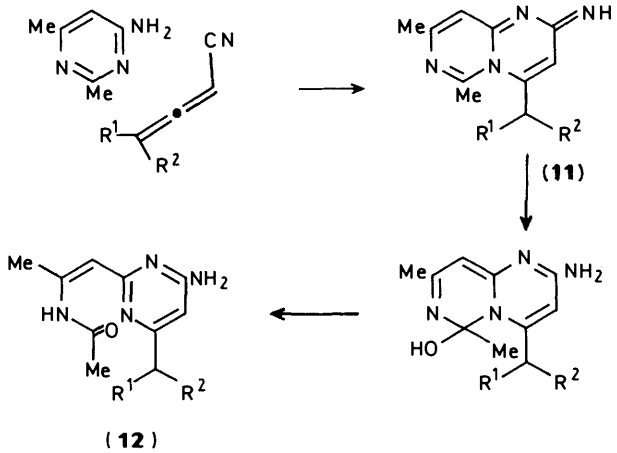


(7c)

Z-form of hypothetical ketone resulting from attack of water at C-4

a]pyrimidine hydrochlorides by heating with allenic nitriles in ethanol and other solvents (*cf.* experiments with 2-aminopyridine hydrochlorides[2]). These all foundered because the hydrochloride is virtually insoluble in non-aqueous solvents and mainly starting materials were recovered. However, mass spectral data and t.l.c. showed that 10—20% of the pyrimido[1,2-*a*]pyrimidine hydrochlorides were formed but these could not be separated from the starting pyrimidine hydrochloride. Treatment of the mixture with ethanolic sodium carbonate gave the corresponding aldehyde (**5**). Similarly attempts to prepare the internally stabilised hydroxypyrimido[1,2-*a*]pyrimidines failed as the starting material, 2-amino-4-hydroxy-6-methylpyrimidine, was only sparingly soluble in ethanol and the reaction extremely slow.

4-Amino-2,6-dimethylpyrimidine refluxed in 95% ethanol with allenic nitriles gave a product which showed the spectroscopic characteristics of an amide (**12**), derived from the pyrimido[1,6-*a*]pyrimidine (**11**) by hydrolysis. It shows a ^{13}C carbonyl signal at δ_C 170.7, a ^1H singlet at δ_H 2.168 for the acetamide methyl, a doublet at δ_H 2.454 (J 1 Hz) for the methyl on C-2 (systematic numbering: C-6) coupled with the proton on C-1′ of the side-chain which itself shows a quartet, and mass spectral fission of methyl and acetyl radicals from the relatively stable molecular ion.

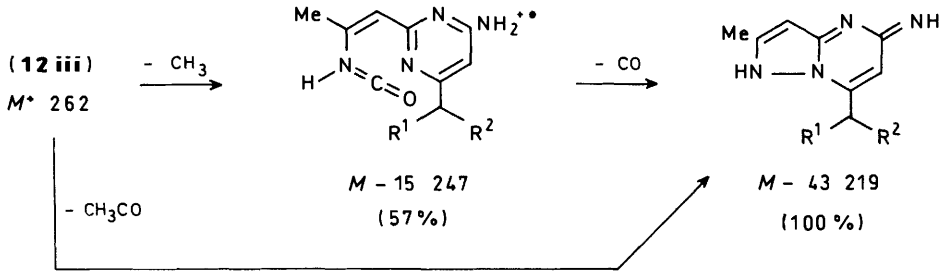


(11)

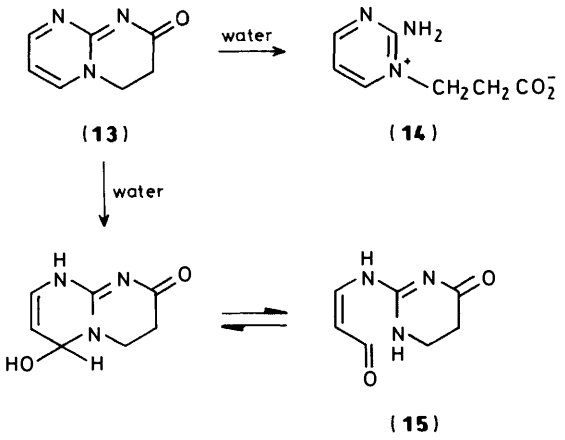
(12)

The hydrolysis of pyrimido[1,2-*a*]pyrimidine or pyrimido[1,6-*a*]pyrimidines has not previously been reported. The hydrolysis of a dihydropyrimido[1,2-*a*]pyrimidine (**13**) by evaporation of an aqueous solution of the hydrochloride with potassium carbonate was described[4] as giving the betaine (**14**) but in the absence of any spectroscopic or other evidence the possibility that the product obtained was the dihydropyrimidinone aldehyde (**15**) cannot be ruled out.*†

* 6,7-Dihydro-2*H*-pyrimido[1,2-*a*]pyrimidine-2,8(9*H*)-dione hydrolyses in boiling water by attack at the 2-position.[5]



Scheme 2.



Experimental

I.r. spectra were determined with Perkin-Elmer 257 and 337 spectrometers, u.v. spectra for ethanolic solutions with Perkin-Elmer 137, Beckman 25, and Cary spectrometers, and n.m.r. spectra with Perkin-Elmer R12, Jeol 60, and Bruker 250 instruments. Allenic nitriles were prepared as previously reported.[6]

3-[(4-*Amino*-6-*s*-*butylpyrimidin*-2-*yl*)*amino*]*propenal* (**5**/**6iia**) *and* 6,9-*dihydro*-6-*hydroxy*-2-*imino*-4-*s*-*butyl*-2H-*pyrimido*-[1,2-a]*pyrimidine* (1,8-*Dihydro*-8-*imino*-6-*s*-*butyl*-4H-*pyrimido*-[1,2-a]*pyrimidin*-4-*ol*) (**4iia**).—4-Methylhexa-2,3-dienenitrile (2.14 g, 0.02 mol) and 2-aminopyrimidine (**1a**) (1.9 g, 0.02 mol) were refluxed in ethanol (95%; 100 ml) for 78 h. Evaporation of solvent and chromatography (alumina, activity 2; eluted with hexane–ethylacetate, 3:2) gave the title compounds [mainly (**6iia**)] as white crystals (1.9 g, 43%), m.p. 175 °C (entry 2, Table); $\nu_{max.}$ 3 350, 3 300, 3 175 (OH, NH, NH_2), 1 610 (C=N), 1 600, and 1 540 cm^{-1}; $\lambda_{max.}$ 250 (ε 10 300), 278 (15 000), and 312 nm (30 900); δ_H[$CDCl_3$ + $(CD_3)_2SO$] 0.84 (3 H, t, CH_2Me), 1.16 (3 H, d, $CHMe$), 1.51 (1 H, sextet, diastereotopic CH_2), 2.454 (1 H, sextet, CH), 5.801 (1 H, dd, $J_{1,2}$ 8.5, $J_{2,3}$ 13.5 Hz, *E*-CH=C*H*CHO), 5.892 (1 H, s, 5-H), 5.972 (2 H, s, NH_2), 8.286 (1 H, br t, *J* 13.5 Hz, HC=C*H*NH), 9.315 (1 H, d, *J* 8.5 Hz, CHO), and 9.704 (1 H, br d, $J \approx 12$ Hz, NH); δ_C 11.92 (CH_3), 19.35 (CH_3), 28.68 (CH_2), 42.66 (*C*HMeEt), 92.02 (CH-N), 108.34 (*C*H-CHO), 150.97 (C-5), 157.33 (C-6), 164.67 (C-4), 174.21 (C-2), and 191.35 (CHO); *m*/*z* 220 (M^+, 20%), 191 (100), 202 (8), and 173 (40).

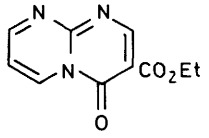
Signals for 6,9-dihydro-6-hydroxy-2-imino-4-s-butylpyrimido[1,2-*a*]pyrimidine (**4iia**) (for proportions see Table); δ_H 3.25 (br s, OH), 5.20 (d, CH=C*H*CHOH), 7.97 (br td, CH=C*H*NH), and 9.91 (br d, NH); δ_C 97.63 (CHOH), 99.02 (CH=), and 142.63 (NCH=); *m*/*z* 202 (M^+ − 18, 8%) and 173 (M^+ − 18 − 29, 40). Signals for the *Z*-isomer (**5iia**) (for proportions see Table); δ_H 9.375 (dd, CH=CHC*H*O) and 12.1 (br s, NH); δ_C 190.37 (HC=O).

Compounds for entries 1 and 3—10 of the Table were prepared similarly and had ^1H and ^{13}C n.m.r. and mass spectra in complete accord with their different side chains.

2-(2-*Acetamidoprop*-1-*enyl*)-4-*amino*-6-*s*-*butylpyrimidine* (**12ii**).—4-Amino-2,6-dimethylpyrimidine (2.46 g, 0.02 mol) and 4-methylhexa-2,3-dienenitrile (2.14 g, 0.02 mol) were heated under reflux in ethanol (96%; 100 ml) for 98 h, after which time 50% of the starting material had reacted as monitored by t.l.c. Evaporation and chromatography gave recovered starting pyrimidine (1.1 g) and the *title compound* (2.1 g, 42%), m.p. 99 °C; R_F 0.57 (benzene–ethyl acetate 3:2) (Found: C, 62.7; H, 7.9; N, 22.5. $C_{13}H_{20}N_4O$ requires C, 62.9; H, 8.07; N, 22.58%); $\nu_{max.}$ 3 180 and 3 300, 3 320, 3 350 cm^{-1} (NH, NH_2); $\lambda_{max.}$ 204 (9 000), 254 (9 600), 288 (10 500), and 304 nm (10 500); $\lambda_{max.}^{EtOH+HCl}$ 205 (10 500), 256 (7 400), and 320 nm (16 600); δ_H 0.82 (3 H, t, $MeCH_2$), 1.22 (3 H, d, *Me*CH), 1.3—1.9 (3 H, m, CH_2CH), 2.12 (3 H, s, Ac), 2.40 (3 H, s, MeC=C), 4.80 (2 H, br s, NH_2, disappears with D_2O), 5.30 (1 H, s, C*H*=CMe), 6.00 (1 H, s, 5-H), and 12.80 (1 H, s, CONH • • • N=, disappears with D_2O); *m*/*z* 248 (M^+, 248).

2-(2-*Acetamidoprop*-1-*enyl*)-4-*amino*-6-(1-*ethylpropyl*)-*pyrimidine* (**12iii**).—4-Amino-2,6-dimethylpyrimidine (2.46 g, 0.02 mol) and 4-ethylhexa-2,3-dienenitrile (2.42 g, 0.02 mol) were heated under reflux in ethanol (96%; 150 ml for 78 h) and the reaction was monitored by t.l.c. to show that 45% of starting material had reacted. Evaporation and chromatography gave recovered starting material (1.3 g) and the *title compound* (1.9 g, 36.3%), m.p. 140 °C; R_F 0.47 (benzene–ethyl acetate 3:2) (Found: C, 64.1; H, 8.4; N, 21.2. $C_{14}H_{22}N_4O$ requires C, 64.12; H, 8.40; N, 21.37%); $\nu_{max.}$ 3 420, 3 340, 3 160 cm^{-1} (NH_2 + NH); $\lambda_{max.}$ 203 (11 500), 254 (11 000), 290 (11 900), and 304 nm (11 900); $\lambda_{max.}^{EtOH+HCl}$ 204 (14 000), 254 (7 700), and 322 nm (18 000); δ_H 0.836 [6 H, t, $(MeCH_2)_2$], 1.690 [4 H, quin, $(CH_2Me)_2$], 2.168 (3 H, s, Ac), 2.290 (1 H, quin, CH_2CHCH_2), 2.454 (3 H, d, *J* 1 Hz, *Me*C=CH), 4.751 (2 H, br s, NH_2), 5.339 (1 H, q, *J* 1 Hz, C*H*=CMe), 5.983 (1 H, s, 5-H), and 12.826 (1 H, br s, NH • • • N=); δ_C 12.12 ($MeCH_2$)$_2$, 22.2 (*Me*CO), 25.38 (*Me*C=), 27.63 (2 × CH_2), 51.22 (*C*HEt$_2$), 99.73 (*C*H=CMe), 106.59

† A. Richardson and F. J. McCarty (*J. Med. Chem.*, 1972, **15**, 1203) prepared a pyrimido[1,2-*a*]pyrimidone and proposed the structure I. However, no evidence was presented which would exclude structure II.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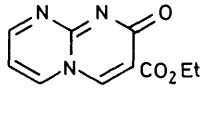
(II)

(C-5), 146.86, 162.71, 165.16 and 168.63 [*C*(Me)=C, C-4, C-6, and C-2], 170.74 (CO); *m/z* 262 (M^+, 31%), 247 ($M^+ - 15$, 57), 234 (24), and 219 (37).

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