212. *Some* 2 : 6-*Diamino- and* 2-*Amino*-6-*hydroxy-derivatives of* 5-*Aryl*-4 : 5-*dihydropyrimidines. A New Synthesis of* 4-*Alkyl*-5-*arylpyrimidines.*

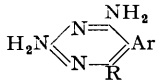
By GEORGE H. HITCHINGS, PETER B. RUSSELL, and NORMAN WHITTAKER.

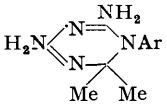
α-*cyclo*Alkylidene-α-arylacetonitriles condense with guanidine to give 2 : 6-diamino-5-aryl-4 : 5-dihydropyrimidine-4-*spirocyclo*alkanes (VII; R = NH_2). Where the aryl group is *p*-chlorophenyl it has been shown that the rate of formation of the diaminodihydropyrimidines is dependent on the size of the *cyclo*alkane ring. The mechanism of this reaction is discussed. The diaminodihydropyrimidines are readily hydrolysed by mineral acid to the corresponding 2-amino-6-hydroxy-derivatives (VII; R = OH). Analogous dihydropyrimidines (III), some of which have strong antimalarial activity, are also obtained from ββ-dialkyl-α-arylacrylonitriles. Guanidine condenses with α-arylacrylonitriles or their β-substituted derivatives, or a mixture of an aldehyde and an arylacetonitrile, to give 2-amino-5-aryl-4 : 5-dihydro-6-hydroxypyrimidines (XIV), which are dehydrogenated by sulphur to the 2-amino-5-aryl-6-hydroxypyrimidines (XV). With aqueous ammonia at 155°, 5-*p*-chlorophenyl-4-ethyl-2 : 6-dimercaptopyrimidine gave a mixture of isomeric aminomercaptopyrimidines.

A SERIES of 2 : 4-diamino-6-alkyl-5-arylpyrimidines (I; R = alkyl) has recently shown outstanding activity against experimental malaria infections in mice and chicks.[1] Moreover, 2 : 4-diamino-5-*p*-chlorophenyl-6-ethylpyrimidine (Daraprim) (I; Ar = *p*-C_6H_4Cl,

[1] Falco, Goodwin, Hitchings, Rollo, and Russell, *Brit. J. Pharmacol.*, 1951, **6**, 185.

R = Et) has value in the chemotherapy of human malarias.[2] The similarity in structure of these pyrimidines to 4 : 6-diamino-1-*p*-chlorophenyl-1 : 2-dihydro-2 : 2-dimethyl-1 : 3 : 5-triazine (II; Ar = *p*-C_6H_4Cl), the antimalarial metabolite[3] of proguanil (Paludrine), prompted an investigation of a possible synthesis of some related 5-aryl-1 : 5-dihydropyrimidine derivatives (III).


(I)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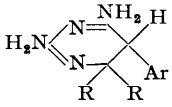
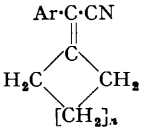

(III)

Benzophenone, *cyclo*hexanone, and *cyclo*pentanone are known to condense readily with phenylacetonitrile in alkaline solution to give αββ-triphenylacrylonitrile and α-*cyclo*alkylidene-α-phenylacetonitriles.[4] By this method acetone, diethyl ketone, benzophenone, and some cyclic ketones have now been condensed with *p*-chlorophenylacetonitrile and, in a few instances, with 3 : 4-dichlorophenylacetonitrile and *p*-methoxyphenylacetonitrile, to give the corresponding compounds (IV; R = alkyl or Ph) and (V; n = 2—5); it was not possible to prepare the *cyclo*butane (V; Ar = *p*-C_6H_4Cl; n = 1). There was no evidence to show that any isomeric *cyclo*alk-1-enylarylacetonitriles (VI) were present in the products derived from the cyclic ketones. The acrylonitrile derivatives (IV) and (V) have a light absorption in the ultraviolet characteristic of a styrene structure (see Table 2).


(IV)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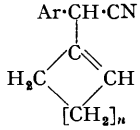
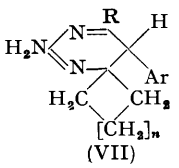
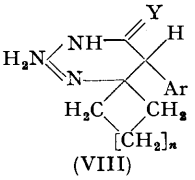
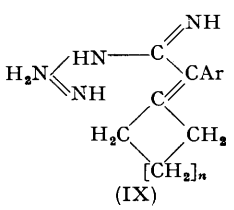
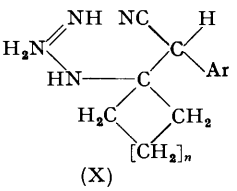

(VI)

The *cyclo*alkylidenearylacetonitriles (V) condensed with guanidine, to give crystalline basic products which are formulated as spirans (VII; R = NH_2). The presence of only an inflexion at *ca.* 245 mμ in the ultraviolet absorption of these products supports this representation rather than that of monocyclic iminoacylguanidines (IX), and structure (X) is unlikely since this type of compound should cyclise readily to the favoured structure (VII; R = NH_2). The diaminodihydropyrimidines (VII; R = NH_2) are stable to alkali but are readily and quantitatively hydrolysed by aqueous mineral acid to the 4-hydroxy-analogues (VII; R = OH). This lability to acid is not surprising since the compounds may be regarded as cyclic iminoacylguanidine derivatives, and imino-*p*-toluoylguanidine,


(VII)


(VIII)


(IX)


(X)

for example, is readily hydrolysed to *p*-toluoylguanidine.[5] Although the two series of dihydropyrimidines have been formulated as (VII; R = NH_2 or OH) they may equally exist in the imino- and keto-forms (VIII; Y = NH or O). In fact, this ready hydrolysis suggests that (VIII) (or a similar prototropic modification) may be the correct formulation.

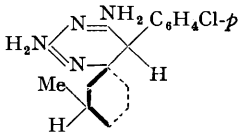
[2] Hitchings, *Trans. Roy. Soc. Trop. Med. Hyg.*, 1952, **46**, 467; Rollo, *ibid.*, p. 485; Coatney, Myatt, Hernandez, Jefferey, and Cooper, *ibid.*, p. 496; *Amer. J. Trop. Med. Hyg.*, 1953, **2**, 777.

[3] Carrington, Crowther, Davey, Levi, and Rose, *Nature*, 1951, **168**, 1080.

[4] Stobbe and Zeitschel, *Ber.*, 1901, **34**, 1963; Birch and Kon, *J.*, 1923, **123**, 2440; Jackman, Nachod, and Archer, *J. Amer. Chem. Soc.*, 1950, **72**, 716; cf. Harding and Haworth, *J.*, 1910, **97**, 486; Jackman, Bohlen, Nachod, Tullar, and Archer, *J. Amer. Chem. Soc.*, 1949, **71**, 2301.

[5] Russell and Hitchings, *J. Amer. Chem. Soc.*, 1950, **72**, 4922.

The structures (VII) and (VIII) contain an asymmetric carbon atom at position 5 of the pyrimidine ring, but attempts to resolve a representative member (VII; Ar = *p*-C_6H_4Cl, R = NH_2, *n* = 3) failed. The tautomeric possibilities in this type of compound are, however, such that racemisation might occur. When the compound (XI) was prepared, the crystalline product recrystallised very slowly and incompletely from supersaturated methanolic solutions, suggesting that it was a mixture of stereoisomers, since the micro-analytical data agreed well with those calculated for the compound : this compound contains three asymmetric centres and four racemates are therefore possible.



(XI)

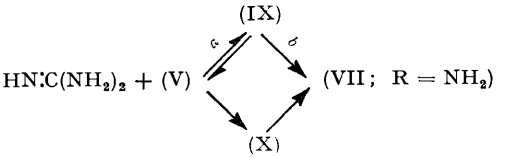
The influence of the size of the *cyclo*alkylidene ring of the nitriles (V; Ar = *p*-C_6H_4Cl, *n* = 2—5) on their rate of condensation with guanidine is quite marked. Table 1 gives the percentage conversions into the dihydropyrimidines (VII; Ar = *p*-C_6H_4Cl, R = NH_2) under standard conditions : conversion is readiest with the *cyclo*hexylidene compound.

TABLE 1. *Conversion (and recovery) of the nitriles* (V; Ar = *p*-C_6H_4Cl) *into the pyrimidines* (VII; R = NH_2).

n	2	3	4	5
2 Hr. heating : conversion (%)	50 *	68	28	7
,, recovery (%)	40	†	66	48
18 Hr. heating : conversion (%)	88 *	94	75	39

* Isolated as the sparingly soluble naphthalene-2-sulphonate. † An oil.

This reaction involves an increase in the co-ordination number of the β-carbon atom of the nitrile (V) from three to four, and it has been shown by Brown and his co-workers [6] that several reactions where this condition holds are favoured by rings of six carbon atoms, in comparison with those of five and seven. Although the comparison of reaction velocities through the yields of products obtained is admittedly open to error, the results suggest that in our condensation the rate-determining step consists of an addition reaction at the ethylenic bond. Whether this addition follows, or precedes, addition at the nitrile group is, however, not known. If reaction involved the intermediate (IX), step (*a*) would then be fast in relation to (*b*), but since large proportions of nitrile (V) were recovered after insufficient periods of reaction, step (*a*) would then have to be reversible also. A reversible reaction of this type seems not unlikely, however, by analogy with the reaction of guanidine with *p*-tolunitrile.[5]

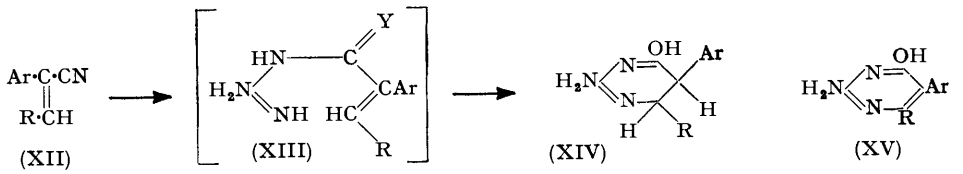


For the preparation in quantity of the diaminospiran (VII; Ar = *p*-C_6H_4Cl, R = NH_2, *n* = 3) it proved more convenient to condense *p*-chlorophenylacetonitrile with *cyclo*hexanone and guanidine directly. The 5-(3 : 4-dichlorophenyl) and 5-(2 : 4 : 5-trichlorophenyl) analogues were also obtained in good yield by this method, but direct condensation of *cyclo*pentanone or *cyclo*heptanone with *p*-chlorophenylacetonitrile and guanidine gave only small yields of the required compounds, contaminated with substantial quantities of *p*-chlorophenylacetamide.

α-*p*-Chlorophenyl-ββ-diphenylacrylonitrile (IV; Ar = *p*-C_6H_4Cl, R = Ph) was unchanged after being heated with alcoholic guanidine, but under these conditions the ββ-dialkyl-α-arylacrylonitriles (IV; Ar = *p*-C_6H_4Cl or 3 : 4-$C_6H_3Cl_2$, R = Me or Et) gave viscous oily bases which are formulated as (III) These bases formed crystalline hydrochlorides but, like the related spirans, they were hydrolysed readily and quantitatively by aqueous mineral acid to the corresponding 6-hydroxy-derivatives.

[6] Brown, Fletcher, and Johannesen, *J. Amer. Chem. Soc.*, 1951, **73**, 212.

Condensation of urea with acrylic acid and α-methylacrylic acid gives the dihydro-derivatives of uracil and thymine respectively.[7] Dihydropyrimidines have also been prepared [8] by condensation of urea with an aldehyde and a β-keto-ester. It seemed possible that *cyclo*hexanone would condense similarly with *p*-chlorophenylacetonitrile and urea in the presence of sulphuric acid, but only a mixture which contained no chlorine was isolated. Again, it was thought that a β-substituted α-arylacrylonitrile (XII) and guanidine might give a 2 : 6-diaminopyrimidine. However, when 2-*p*-chlorophenylpent-2-enonitrile (XII; Ar = *p*-C_6H_4Cl, R = Et) was heated with alcoholic guanidine, ammonia was evolved and the product was the 2-amino-6-hydroxypyrimidine (XIV; Ar = *p*-C_6H_4Cl, R = Et). The behaviour of α-*p*-chlorophenyl- (XII; Ar = *p*-C_6H_4Cl, R = H) and αβ-diphenyl-acrylo-



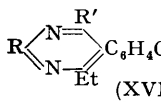
nitrile (XII; Ar = R = Ph) was analogous, the 2-amino-6-hydroxy-derivatives being obtained. This reaction probably proceeds with the intermediate formation of iminoacylguanidines (XIII; Y = NH), hydrolysis to acylguanidines (XIII; Y = O) preceding ring closure. To obtain the 2-amino-6-hydroxypyrimidines (XIV) in quantity, the preliminary preparation of the acrylonitrile derivatives (XII) was not essential since direct condensation of guanidine with the appropriate arylacetonitrile and aldehyde afforded satisfactory yields of the pyrimidines.

Fischer and Roeder [7] prepared uracil and thymine by brominating the corresponding dihydro-derivatives and then removing hydrogen bromide with pyridine or alkali. The dihydropyrimidines (XIV) were conveniently dehydrogenated by sulphur at 180—190°, giving the corresponding 2-amino-5-aryl-6-hydroxypyrimidines (XV) in good yield. Dehydrogenation by chloranil was less satisfactory. Four compounds of type (XV) were obtained in this manner, of which three were known. The only other method available for the preparation of 4-alkylpyrimidines of type (XV) is the reaction of α-aryl-β-keto-esters with guanidine in 20% oleum.[9] These esters do not react with guanidine base [10] but it is now found that, by heating ethyl 2-*p*-chlorophenyl-3-oxopentanoate with guanidine carbonate in alcohol, a minute yield of 2-amino-5-*p*-chlorophenyl-4-ethyl-6-hydroxypyrimidine (XV; Ar = *p*-C_6H_4Cl, R = Et) is obtained. A further new procedure for the preparation of such compounds is hydrolysis of the 2 : 4-diaminopyrimidines, but the yields are only moderate.

2-Amino-5-*p*-chlorophenyl-4-ethyl-6-hydroxypyrimidine (XV; Ar = *p*-C_6H_4Cl, R = Et) was successively acetylated, chlorinated, and heated with alcoholic ammonia at 160°, yielding 2 : 4-diamino-5-*p*-chlorophenyl-6-ethylpyrimidine (XVI; R = R′ = NH_2) (Daraprim). This route to Daraprim has also been described recently [9] by the workers of Rhône-Poulenc who began their synthesis with 2-amino-5-*p*-chlorophenyl-4-ethyl-6-hydroxypyrimidine prepared from ethyl 2-*p*-chlorophenyl-3-oxopentanoate. A further method is to heat 2-amino-5-*p*-chlorophenyl-4-ethyl-6-mercaptopyrimidine (XVI; R = NH_2, R′ = SH) with alcoholic ammonia at 180°. This thiol was obtained by treating the corresponding 6-hydroxypyrimidine with phosphorus pentasulphide in tetralin at *ca.* 170°. Under similar conditions the dihydro-compound (XIV; Ar = *p*-C_6H_4Cl, R = Et) was also converted into the thiol (XVI; R = NH_2, R′ = SH) in moderate yield, dehydrogenation accompanying and, probably, preceding introduction of sulphur. When either of these 6-hydroxy-derivatives was treated with phosphorus pentasulphide at higher temperatures (190°), 5-*p*-chlorophenyl-4-ethyl-2 : 6-dimercaptopyrimidine (XVI; R = R′ = SH) alone

[7] Fischer and Roeder, *Ber.*, 1901, **34**, 3751.
[8] Biginelli, *Ber.*, 1891, **24**, 1317; Folkers and Johnson, *J. Amer. Chem. Soc.*, 1932, **54**, 3751; 1933, **55**, 1140, 2886, 3784.
[9] Jacob. B.P. 730,472.
[10] Russell and Hitchings, *J. Amer. Chem. Soc.*, 1951, **73**, 3763.

resulted, and at intermediate temperatures mixtures of the 2-amino-6-mercapto- and the 2 : 6-dimercapto-pyrimidine were produced. By heating 2 : 4-diamino-5-*p*-chlorophenyl-6-ethylpyrimidine (XVI; R = R′ = NH_2) with phosphorus pentasulphide in tetralin at 190°, 5-*p*-chlorophenyl-4-ethyl-2 : 6-dimercaptopyrimidine (XVI; R = R′ = SH) was again obtained but in small yield. The dithiol with aqueous ammonia at 155° gave a 1 : 4 mixture of 2-amino-5-*p*-chlorophenyl-4-ethyl-6-mercaptopyrimidine (XVI; R = NH_2, R′ = SH) with the isomeric derivative (XVI; R = SH, R′ = NH_2). The formation of the 2-aminopyrimidine is surprising since 2 : 4-dimercaptopyrimidines previously examined give the 4-amino-2-mercapto-derivatives exclusively under these conditions.[11] Since the completion of our work the compound (XVI; R = SH, R′ = NH_2) has been prepared by another route.[12] The aminomercaptopyrimidines (XVI; R = NH_2, R′ = SH, and *vice versa*) with methyl iodide and alkali yielded the respective methylthio-compounds. Surprisingly, neither of these reacted with alcoholic ammonia at 160—170°, or with amines, but they were reduced by Raney nickel to 2- and 4-amino-5-*p*-chlorophenyl-6-ethylpyrimidine (XVI; R = NH_2, R′ = H and *vice versa*).



(XVI)

Our colleagues, Dr. L. G. Goodwin and Mr. I. M. Rollo, report that 2 : 6-diamino-5-(3 : 4-dichlorophenyl)-4 : 5-dihydro-4 : 4-dimethylpyrimidine is active against *Plasmodium gallinaceum* in chicks at 1 mg./kg. (inactive at 0·1mg./kg.) and against *P. berghei* in mice at 10 mg./kg. (inactive at 1 mg./kg.) and that its 5-*p*-chlorophenyl analogue is almost as active against these plasmodia [Pyrimethamine (Daraprim) (I; Ar = *p*-C_6H_4Cl, R = Et) is active against both *P. gallinaceum* and *P. berghei* at 0·1 mg./kg., but inactive at 0·01 mg./kg.]. In contrast, the 4 : 4-diethyl compounds have only a trace of activity against *P. gallinaceum* at 200 mg./kg., and the spirans (VII; R = NH_2) have no antimalarial activity. This is not surprising, for by replacing the *iso*propyl group of proguanil—in effect, the methyl groups of its metabolite (II; Ar = *p*-C_6H_4Cl)—by a larger substituent a similar decrease in antimalarial activity results.[13] It is noteworthy that these 4 : 4-dialkyl-4 : 5-dihydropyrimidines showed no activity against a strain of *P. gallinaceum* which had been made resistant to Pyrimethamine.

Our colleague, Dr. R. A. Neal, finds that the 4 : 4-dialkyl-2 : 6-diamino-5-aryl-4 : 5-dihydropyrimidines and a number of the spiran analogues (VII; R = NH_2) are active against *Entamoeba histolytica* in rats given 6 daily oral doses of 250 mg./kg. One of these compounds, 2 : 6-diamino-5-(3 : 4-dichlorophenyl)-4 : 5-dihydro-4 : 4-dimethylpyrimidine, is active at 125 mg./kg.

Experimental

Acrylonitriles (IV) *and* (V) (*Table* 2).—A mixture of equimolecular quantities of the appropriate arylacetonitrile and ketone was added to a solution of one atomic equiv. of sodium in 6—7 equivs. of anhydrous ethanol. The solution was usually heated under reflux for 30 min., cooled (crystallisation occurred in some cases), and diluted with water. Sulphuric acid was added to pH 5—6, the product extracted with ether, the extract washed with water and dried (Na_2SO_4), and the ether removed. In some instances the residual oil crystallised spontaneously and one crystallisation (method A) yielded the pure acrylonitrile; in the other cases the residual oil was distilled under reduced pressure, and the fraction containing the product was dissolved in light petroleum (b. p. 60—80°), or benzene–light petroleum, filtered from arylacetamide, and then poured through a short column of activated alumina. After removal of the solvent from the eluate, some of the residual acrylonitriles could then be crystallised (method B), but others were oils which were finally redistilled (method C).

In addition to the compounds listed in Table 2, 1-(p-*chlorophenylcyanomethylene*)-3-*methyl*-cyclo*hexane* was prepared from *p*-chlorophenylacetonitrile and 3-methyl*cyclo*hexanone and was purified by method C. It was a pale yellow oil (50%) (presumably a mixture of *cis*- and *trans*-isomers), b. p. 133—134°/0·17 mm., part of which crystallised at 0° during several weeks (Found : C, 73·1; H, 6·75; Cl, 14·1. $C_{15}H_{16}NCl$ requires C, 73·3; H, 6·5; Cl, 14·45%).

[11] Russell, Elion, Falco, and Hitchings, *J. Amer. Chem. Soc.*, 1949, **71**, 2279.
[12] Baker, Schaub, Joseph, McEvoy, and Williams, *J. Org. Chem.*, 1953, **18**, 133.
[13] Curd and Rose, *J.*, 1946, 729.

TABLE 2. ββ-*Dialkyl(or diaryl)*-α-*arylacrylonitriles* (IV) *and* (*arylcyanomethylene*)cyclo*alkanes* (V).

Ar	R	Method of purifn.	Cryst. from	M. p. or b. p./mm.	Yield (%)	Formula	Found (%) C	H	N	Cl	Required (%) C	H	N	Cl	$\lambda_{max.}$ (mμ) †	ε
Nitriles (IV)																
p-C_6H_4Cl	Me	C	—	162—164°/12	42	$C_{11}H_{10}NCl$	68·6	5·15	7·15	18·45	69·0	5·2	7·3	18·55	247·5	12,800
p-C_6H_4Cl	Et	C	—	162—169°/8	33	$C_{13}H_{14}NCl$	70·8	6·4	6·3	16·45	71·1	6·4	6·4	16·2	246	11,500
3 : 4-$C_6H_3Cl_2$	Me *	A	EtOH	106—107°	78	$C_{11}H_9NCl_2$	58·2	4·35	6·15	31·45	58·5	4·0	6·2	31·4	250	13,000
3 : 4-$C_6H_3Cl_2$	Et *	B	MeOH	47—49	21	$C_{13}H_{13}NCl_2$	61·7	5·15	5·5	27·95	61·5	5·1	5·5	28·0	249	11,000
p-C_6H_4Cl	Ph	A	EtOH	143—144	15	$C_{21}H_{14}NCl$	80·3	4·6	4·15	—	79·9	4·45	4·45	—	239 319	25,200 16,100
Nitriles (V)																
Ar	*n*															
p-C_6H_4Cl	2	A	EtOH	75—76	31	$C_{13}H_{12}NCl$	71·6	5·4	6·45	16·3	71·7	5·5	6·45	16·3	260	17,000
p-C_6H_4Cl	3	B	MeOH	43—44	37	$C_{14}H_{14}NCl$	72·65	5·9	5·95	15·4	72·6	6·05	6·05	15·35	250	15,200
p-C_6H_4Cl	4	A	EtOH	117—118	53	$C_{15}H_{16}NCl$	73·55	6·7	5·75	14·2	73·3	6·5	5·7	14·45	250	12,500
p-C_6H_4Cl	5	B	MeOH	63—64	21	$C_{16}H_{18}NCl$	73·9	6·95	5·35	—	74·0	6·95	5·4	—	250	12,000
3 : 4-$C_6H_3Cl_2$	2 *	A	EtOH	81—82	55	$C_{13}H_{11}NCl_2$	61·8	4·6	5·6	28·3	61·9	4·35	5·55	28·2	261	14,400
3 : 4-$C_6H_3Cl_2$	3	B	MeOH	64—65	45	$C_{14}H_{13}NCl_2$	63·1	5·15	5·3	26·05	63·2	4·9	5·25	26·7	250	13,500
p-MeO·C_6H_4	3	C	—	128°/0·05	15	$C_{15}H_{17}ON$	79·35	7·3	6·15	—	79·3	7·5	6·15	—	265	8,500

* Prepared by setting the mixed reactants aside for 24 hr. at room temperature. † In EtOH.

TABLE 3. 2 : 6-*Diamino*-5-*aryl*-4 : 5-*dihydropyrimidine*-4-spirocyclo*alkanes* (VII; R = NH_2) *and* 4 : 4-*dialkyl*-2 : 6-*diamino*-5-*aryl*-4 : 5-*dihydropyrimidines* (III).

Ar	*n*	Compd.	Cryst. from	M. p.*	Formula †	Found (%) C	H	N	N ‡	Cl	Required (%) C	H	N	N ‡	Cl
Spirans (VII; R = NH_2).															
Ph	3	Base	Aq.MeOH	135°	$C_{15}H_{20}N_4$	70·1	7·8	—	—	—	70·4	7·8	—	—	—
p-C_6H_4Cl	2	Base	Aq.MeOH	153	$C_{14}H_{17}N_4Cl,H_2O$	56·7	6·2	—	—	—	56·9	6·4	—	—	—
		$C_{10}H_7$-2-SO_3H	Aq.MeOH	246—247	$C_{24}H_{25}O_3N_4SCl$	(S, 6·4)		11·75	2·95	7·30	(S, 6·6)		11·55	2·90	7·35
p-C_6H_4Cl	3	Base	MeOH	157—159	$C_{15}H_{19}N_4Cl,CH_3·OH$	59·45	6·75	17·3	—	10·7	59·5	7·15	17·35	—	11·0
p-C_6H_4Cl	4	Base	Aq.MeOH	179—181	$C_{16}H_{21}N_4Cl,\frac{1}{2}H_2O$	61·3	7·15	17·55	—	—	61·3	7·0	17·85	—	—
p-C_6H_4Cl	5	Base	Aq.MeOH	181—182	$C_{17}H_{23}N_4Cl,\frac{1}{2}H_2O$	62·05	7·5	16·7	—	—	62·3	7·35	17·1	—	—
3 : 4-$C_6H_3Cl_2$ ...	2	HCl	H_2O	186—188	$C_{14}H_{17}N_4Cl_3,H_2O$	46·4	4·9	15·15	3·85	29·2	46·0	5·2	15·3	3·85	29·2
3 : 4-$C_6H_3Cl_2$ ...	3	Base	MeOH	166—167	$C_{15}H_{18}N_4Cl_2,CH_3·OH$	54·2	6·1	15·85	—	—	53·8	6·15	15·7	—	—
2 : 4 : 5-$C_6H_2Cl_3$	3	Base	MeOH	218—219	$C_{15}H_{17}N_4Cl_3$	49·5	4·5	15·45	3·75	29·5	50·1	4·75	15·6	3·9	29·6
p-MeO·C_6H_4 ...	3	Base	Aq.MeOH	164—165	$C_{16}H_{22}ON_4$	66·75	7·7	19·65	4·6	—	67·2	7·7	19·6	4·9	—
Ar	R														
Derivatives (III).															
p-C_6H_4Cl	Me	HCl	—	244—245	$C_{12}H_{16}N_4Cl_2$	50·4	5·75	19·1	4·6	24·4	50·2	5·6	19·5	4·9	24·75
p-C_6H_4Cl	Et	HCl	H_2O	172	$C_{14}H_{20}N_4Cl_2$	53·8	6·1	17·5	4·6	22·5	53·3	6·35	17·8	4·45	22·5
		β-$C_{10}H_7·SO_3H$	EtOH	244—245	$C_{24}H_{27}O_3N_4SCl$	(S, 6·3)		11·1	—	7·15	(S, 6·6)		11·5	—	7·3
3 : 4-$C_6H_3Cl_2$ ...	Me	HCl	H_2O	278—280	$C_{12}H_{15}N_4Cl_3$	44·65	4·95	17·65	4·25	32·55	44·8	4·65	17·4	4·35	33·15
3 : 4-$C_6H_3Cl_2$ ...	Et	HCl	H_2O	180	$C_{14}H_{19}N_4Cl_3$	48·3	5·4	15·95	3·95	29·9	48·1	5·45	16·05	4·0	30·5

* M.p.s accompanied by varying degrees of decomp. † Compounds shown as solvated were dried at room temperature; others were dried at 100° in a vacuum. ‡ These are labile N values, determined by hydrolysis with 2N-sulphuric acid in the steam-bath during 30 min., then addition of an excess of sodium hydroxide and determination of the ammonia liberated (micro-Kjeldahl).

2 : 6-*Diamino*-5-*aryl*-4 : 5-*dihydropyrimidine*-4-spirocyclo*alkanes* (VII; R = NH_2) (Table 3). —(*a*) The nitrile (V) was treated with 1·1 equivs. of 0·8N-alcoholic guanidine (prepared from guanidine hydrochloride and alcoholic sodium ethoxide), the mixture being heated under reflux for 18 hr., cooled, and diluted slowly with *ca.* 3 volumes of water, with seeding. Light petroleum (b. p. 60—80°), or a little benzene, was then added, with shaking, to dissolve any unchanged starting material and, after 3 hr., the crystalline product was collected and washed with water and benzene. The spirans (VII; R = NH_2, *n* = 3, 4, and 5) crystallised from methanol or aqueous methanol in a solvated form, but the analogues where *n* = 2 did not crystallise readily and were converted into the naphthalene-2-sulphonate or hydrochloride by adding 1 equiv. of concentrated aqueous naphthalene-2-sulphonic or hydrochloric acid to an ice-cooled solution of the base in aqueous alcohol or acetone respectively. With one exception (VII; Ar = *p*-C_6H_4Cl, R = NH_2, *n* = 5), all the spirans were obtained in good yield (see also Table 1). 2 : 6-*Diamino*-5-p-*chlorophenyl*-4 : 5-*dihydropyrimidine*-4-spiro-(3-*methyl*cyclo*hexane*) crystallised from methanol in colourless prisms, m. p. 161—163° (effervescence) (Found : C, 60·15; H, 7·4; N, 16·65. $C_{16}H_{21}N_4Cl,CH_3{\cdot}OH$ requires C, 60·65; H, 7·45; N, 16·65%).

(*b*) A mixture of equimolar quantities of *p*-chlorophenylacetonitrile and *cyclo*hexanone was added to 1 equiv. of 0·8N-alcoholic guanidine. The solution was heated under reflux for 3 hr., cooled, and diluted slowly with water, with seeding, giving the spiran (VII; Ar = *p*-C_6H_4Cl, R = NH_2, *n* = 3) (47%). The spirans (VII; Ar = 3 : 4-$C_6H_3Cl_2$ and 2 : 4 : 5-$C_6H_2Cl_3$, R = NH_2, *n* = 3) were obtained similarly, in yields of 52% and 45% respectively. 2 : 6-*Diamino*-5-p-*chlorophenyl*-4 : 5-*dihydropyrimidine*-4-spiro-(4-*methyl*cyclo*hexane*), prepared from *p*-chlorophenylacetonitrile, 4-methyl*cyclo*hexanone, and guanidine, crystallised from methanol in solvated colourless prisms, m. p. 166—168° (effervescence) (Found : C, 60·2; H, 7·75; N, 16·85%).

4 : 4-*Dialkyl*-2 : 6-*diamino*-5-*aryl*-4 : 5-*dihydropyrimidines* (III) (Table 3).—The nitrile (IV) was treated with 1·1 equivs. of 0·8N-alcoholic guanidine, heated under reflux for 24 hr., cooled and diluted with an equal volume of water. The alcohol was then removed under reduced pressure at *ca.* 40°, the cooled (0°) aqueous liquid was decanted from the gum, and the gum was dissolved in dried ($CaCl_2$) acetone. The acetone was then distilled, first at atmospheric pressure, and then under reduced pressure at room temperature, and the residual gum was redissolved in dry acetone. To the ice-cooled acetone solution, concentrated hydrochloric acid was added dropwise, with shaking, to pH 5—6, and after 1 hr. at 0° the crystals of the 4 : 4-dialkyl-2 : 6-diamino-5-aryl-4 : 5-dihydropyrimidine hydrochloride (80—85% yield) were collected and washed with acetone. These hydrochlorides contained both acetone and water of crystallisation and, with one exception, were finally recrystallised from water.

2-*Amino*-5-*aryl*-4 : 5-*dihydro*-6-*hydroxypyrimidine*-4-spirocyclo*alkanes* (VII; R = OH) *and their Monocyclic Analogues* (Table 4).—A solution of 2 : 6-diamino-5-(3 : 4-dichlorophenyl)-4 : 5-dihydropyrimidine-4-*spirocyclo*hexane (16·0 g.) in hot glacial acetic acid (40 ml.) and water

TABLE 4. 2-*Amino*-5-*aryl*-4 : 5-*dihydro*-6-*hydroxypyrimidine*-4-spirocyclo*alkanes* (VII; R = OH) *and* 4 : 4-*dialkyl*-2-*amino*-5-*aryl*-4 : 5-*dihydro*-6-*hydroxypyrimidines* (*B*).

Ar	*n*	Compd.	Cryst. from	M. p.*	Formula	Found (%) C	H	N	Required (%) C	H	N
Spirans (VII; R = OH).											
Ph...	3	Base	Aq. MeOH	307°	$C_{15}H_{19}ON_3,H_2O$	65·7	7·8	—	65·5	7·65	
X ...	2	Base	Aq. MeOH	286	$C_{14}H_{16}ON_3Cl,H_2O$	57·2	6·3	—	56·9	6·1	—
X ...	3	Base	MeOH	307	$C_{15}H_{18}ON_3Cl,MeOH$ [a]	59·25	6·75	12·8	59·4	6·8	13·0
X ...	4	Base	MeOH	301—302	$C_{16}H_{20}ON_3Cl,MeOH$ [b]	60·35	6·8	12·2	60·5	7·1	12·45
Y ...	2	HCl	Dil. HCl	225—227	$C_{14}H_{16}ON_3Cl_3$ [d, e]	48·4	4·7	11·8	48·25	4·6	12·05
Y ...	3	Base	MeOH	316—317	$C_{15}H_{17}ON_3Cl_2$	55·2	5·3	12·95	55·2	5·2	12·9
Aryl	Alkyl										
Derivatives (*B*).											
X ...	Me	Base	H_2O	245—247	$C_{12}H_{14}ON_3Cl,2H_2O$ [c]	50·45	6·3	14·35	50·15	6·25	14·6
X ...	Et	Base	H_2O	246—248	$C_{14}H_{18}ON_3Cl$ [d, f]	—	—	14·7	—	—	15·05

X = *p*-C_6H_4Cl. Y = 3 : 4-$C_6H_3Cl_2$. * With decomp.

[a] Loss on drying: Found, 10·0. Reqd., 9·9%. Found: Cl, 10·95. Reqd.: Cl, 10·95%. [b] Loss on drying: Found, 9·0. Reqd., 9·5%. [c] Loss on drying: Found, 11·9. Reqd., 12·5%. Found: Cl, 12·5. Reqd.: Cl, 12·35%. [d] Dried at 100° *in vacuo* before analysis. [e] Found: Cl, 30·5. Reqd.: Cl, 30·6%. [f] Found: Cl, 12·45. Reqd.: Cl, 12·7%.

(120 ml.) was treated with concentrated hydrochloric acid (20 ml.) and heated under reflux for 20 min. After addition of a slight excess of aqueous sodium hydroxide and cooling, the precipitated crystalline base was collected, washed with water, and then boiled with dilute aqueous sodium hydroxide (*ca.* 1 l.) to convert any remaining hydrochloride into free base. After cooling, the product was again collected, washed with water, dried [14·2 g.; m. p. 325—326° (decomp.)] and digested with hot methanol (1 l.), giving colourless prisms (15·0 g.), m. p. 316—317° (decomp.), containing *ca.* 1 mol. of methanol of crystallisation, of the hydroxy-spiran (VII; Ar = 3 : 4-$C_6H_3Cl_2$, R = OH, n = 3). The crystals lost their solvent of crystallisation during 2 days at room temperature.

The other *hydroxy-spirans* listed in Table 4 were obtained similarly, and in almost quantitative yield, from the corresponding diamines; one of them was characterised as its hydrochloride.

2-p-*Chlorophenylpent-2-enonitrile*.—This compound was obtained from *p*-chlorophenylacetonitrile and propaldehyde by the method used for the phenyl analogue.[14] The product was a mixture of oil and crystals; ethanol was added to dissolve the oil and the crystals were collected and recrystallised from ether–light petroleum, giving colourless cubes of polymeric *nitrile*, m. p. 145° [Found: C, 68·7; H, 5·6; N, 7·5. $(C_{11}H_{10}NCl)_n$ requires C, 68·9; H, 5·2; N, 7·3%]. Evaporation of the alcoholic filtrate yielded crude monomeric nitrile.

α-p-*Chlorophenylacrylonitrile* was prepared by the method used for making α-phenylacrylonitrile.[15] It was a colourless mobile liquid, b. p. 97°/0·25 mm., consisting substantially of the monomer ($\lambda_{max.}$ 262 mμ, ε 6800), but containing some dimer (Found: N, 8·6. C_9H_6NCl requires N, 8·55%). After 4 days at 0° the liquid was viscous (ε 3500, decreasing, after 10 min. at 100°, to 1600).

2-*Amino*-5-*aryl*-4 : 5-*dihydro*-6-*hydroxypyrimidines* (XIV).—(*a*) Crude 2-*p*-chlorophenylpent-2-enonitrile (10·0 g.) was heated in alcoholic guanidine (5·9 g. in 100 ml.) under reflux for 10 hr., during which ammonia was evolved. The alcohol was then removed and the residual solid was washed with ether and recrystallised from ethanol, giving 2-*amino*-5-p-*chlorophenyl*-4-*ethyl*-4 : 5-*dihydro*-6-*hydroxypyrimidine* (7 g.), m. p. 275° (Found: C, 57·0; H, 5·4; N, 16·4. $C_{12}H_{14}ON_3Cl$ requires C, 57·25; H, 5·55; N, 16·7%). This base dissolved in dilute hydrochloric acid and was reprecipitated by adding aqueous alkali.

αβ-Diphenylacrylonitrile [16] (10·0 g.) was heated in alcoholic guanidine (2·9 g. in 50 ml.) under reflux overnight. The cooled solution was treated with dilute aqueous sodium hydroxide (100 ml.), and the precipitated solid was recrystallised from aqueous ethanol, forming colourless prisms (6·7 g.) of 2-*amino*-4 : 5-*dihydro*-6-*hydroxy*-4 : 5-*diphenylpyrimidine*, m. p. 285—286° (Found: C, 72·4; H, 5·3; N, 16·0. $C_{16}H_{15}ON_3$ requires C, 72·5; H, 5·65; N, 15·85%).

2-Amino-5-*p*-chlorophenyl-4 : 5-dihydro-6-hydroxypyrimidine was obtained by reaction of α-*p*-chlorophenylacrylonitrile with guanidine as a crude solid which could not be purified. Its identity was confirmed by dehydrogenation to 2-amino-5-*p*-chlorophenyl-4-hydroxypyrimidine (see below).

(*b*) *p*-Chlorophenylacetonitrile (15·0 g.) and propaldehyde (5·8 g.) were added to alcoholic guanidine (5·9 g. in 150 ml.). The resulting solution was kept at 0° for 1 hr., then warmed gradually to 30° during 2 hr., and finally heated under reflux for 3 hr. Ammonia was liberated. Water (200 ml.) was added to the cooled solution, and the liquid was decanted from the precipitated oil. The oil on being treated with ether gave crystals which recrystallised from ethanol, giving pure 2-amino-5-*p*-chlorophenyl-4-ethyl-4 : 5-dihydro-6-hydroxypyrimidine (10 g.), m. p. 273° undepressed in admixture with material obtained by method (*a*).

Equimolar quantities of phenylacetonitrile, benzaldehyde and guanidine in ethanol in this manner gave 2-amino-4 : 5-dihydro-6-hydroxy-4 : 5-diphenylpyrimidine (30%), m. p. 284°, undepressed in m. p. in admixture with material obtained by method (*a*).

m-Chlorophenylacetonitrile (30·0 g.) and propaldehyde (11·6 g.) were added to alcoholic guanidine (11·8 g. in 200 ml.), and the resulting solution was kept at room temperature for 2 hr., then heated overnight. The cooled solution was diluted with water (600 ml.), and the precipitated solid was collected, washed with ether, and recrystallised from aqueous ethanol, yielding colourless needles (17 g.), m. p. 229—230°, of 2-*amino*-5-m-*chlorophenyl*-4-*ethyl*-4 : 5-*dihydro*-6-*hydroxypyrimidine* (Found: C, 57·5; H, 5·7; N, 16·4%).

2-*Amino*-5-(3 : 4-*dichlorophenyl*)-4-*ethyl*-4 : 5-*dihydro*-6-*hydroxypyrimidine* was obtained by heating 3 : 4-dichlorophenylacetonitrile (18·6 g.), propaldehyde (5·8 g.) and alcoholic guanidine (5·9 g. in 150 ml.) under reflux for 5 hr. and isolating the product as in the previous experiment.

[14] Murray and Cloke, *J. Amer. Chem. Soc.*, 1936, **58**, 2014.
[15] Walker, U.S.P., 2,478,990.
[16] Von Walther, *J. prakt. Chem.*, 1896, **53**, 454.

The recrystallised product (9·0 g.) had m. p. 242° (Found : C, 50·5; H, 4·8; N, 14·5. $C_{12}H_{13}ON_3Cl_2$ requires C, 50·35; H, 4·55; N, 14·7%).

2-*Amino*-5-*aryl*-6-*hydroxypyrimidines* (XV).—(*a*) An intimate mixture of the 2-amino-5-aryl-4 : 5-dihydro-6-hydroxypyrimidine (XIV) with twice its weight of sulphur was heated at 180—190° for 4 hr., hydrogen sulphide being evolved. Unchanged sulphur was extracted from the cooled mixture with carbon disulphide, and the residual solid was dissolved in cold dilute aqueous sodium hydroxide. The solution was treated with charcoal, filtered, and added dropwise to hot dilute acetic acid; the product was precipitated. In this way were prepared : 2-amino-5-*p*-chlorophenyl-4-ethyl-6-hydroxypyrimidine (70%), m. p. 270° [2-acetamido-analogue, m. p. 263—264° (from aqueous ethanol) (Found : C, 57·6; H, 4·9. Calc. for $C_{14}H_{14}O_2N_3Cl$: C, 57·65; H, 4·8%)]; 2-*amino*-4-*hydroxy*-5 : 6-*diphenylpyrimidine*, colourless needles (from ethanol), m. p. 319° (Found : C, 73·0; H, 5·0; N, 16·3. $C_{16}H_{13}ON_3$ requires C, 73·0; H, 4·95; N, 15·95%); 2-amino-5-*p*-chlorophenyl-4-hydroxypyrimidine, m. p. 320° (decomp.) (from ethanol) (identical with an authentic specimen prepared by another route [10]); 2-amino-5-(3 : 4-dichlorophenyl)-4-ethyl-6-hydroxypyrimidine [*2-acetamido-analogue* (42%), m. p. 261° (Found : C, 51·5; H, 4·1. $C_{14}H_{13}O_2N_3Cl_2$ requires C, 51·5; H, 4·0%)].

(*b*) 2 : 4-Diamino-5-*p*-chlorophenyl-6-ethylpyrimidine (12·0 g.), concentrated hydrochloric acid (100 ml.), and water (10 ml.) were heated under reflux during 5 hr. The cooled solution was diluted with water (250 ml.), made alkaline with aqueous sodium hydroxide, and filtered. The filtrate was acidified with acetic acid, giving a white precipitate which was collected and dissolved in cold 2N-sodium hydroxide. The filtered solution was added dropwise to a slight excess of boiling dilute acetic acid, yielding 2-amino-5-*p*-chlorophenyl-4-ethyl-6-hydroxypyrimidine as colourless needles (2·7 g.), m. p. 284°. This material was identified with that obtained by method (*a*) as shown by its ultraviolet absorption and by the properties of its acetyl derivative.

2-*Amino*-5-p-*chlorophenyl*-4-*ethyl*-6-*mercaptopyrimidine* (XVI; R = NH_2, R′ = SH).—A mixture of 2-amino-5-*p*-chlorophenyl-4-ethyl-4 : 5-dihydro-6-hydroxypyrimidine (10·0 g.), phosphorus pentasulphide (25·0 g.), and tetralin (70 ml.) was heated at 170—175°, with stirring, during 2 hr. The cooled liquid was diluted with light petroleum (b. p. 60—80°), and the precipitated solid was collected and dissolved in concentrated aqueous ammonia. The solution was treated with charcoal, filtered, and added to dilute acetic acid, precipitating the *aminomercaptopyrimidine* which crystallised from benzene in pale yellow prisms (5·1 g.), m. p. 231° (Found : C, 53·9; H, 4·7. $C_{12}H_{12}N_3SCl$ requires C, 54·2; H, 4·5%). This compound was obtained in slightly improved yield when 2-amino-5-*p*-chlorophenyl-4-ethyl-6-hydroxypyrimidine was treated with phosphorus pentasulphide under the same conditions.

5-p-*Chlorophenyl*-4-*ethyl*-2 : 6-*dimercaptopyrimidine* (XVI; R = R′ = SH).—When the reaction described above was carried out at 190°, the product was the *dimercaptopyrimidine* which crystallised from benzene in bright yellow prisms (2·7 g.), m. p. 317° (Found : C, 51·0; H, 3·9. $C_{12}H_{11}N_2S_2Cl$ requires C, 51·0; H, 3·9%). The benzene liquors, on being kept for several days, yielded a small quantity (0·2 g.) of 2-amino-5-*p*-chlorophenyl-4-ethyl-6-mercaptopyrimidine, m. p. 229—230°.

When 2 : 4-diamino-5-*p*-chlorophenyl-6-ethylpyrimidine (10·0 g.) was heated with phosphorus pentasulphide (25 g.) in tetralin at 190°, the dimercaptopyrimidine (0·56 g.), m. p. 312—313°, was again obtained.

Reactions with Ammonia.—(a) 2-*Amino*-5-p-*chlorophenyl*-4-*ethyl*-6-*mercaptopyrimidine*. The aminomercaptopyrimidine (2·5 g.) was heated with saturated ethanolic ammonia (50 ml.) in an autoclave at 180° during 16 hr. The solution was evaporated *in vacuo* and the residual solid was shaken with 2N-sodium hydroxide (20 ml.), collected, and purified by reprecipitation from a solution in hot dilute acetic acid with sodium hydroxide. After crystallising from ethanol, the 2 : 4-diamino-5-*p*-chlorophenyl-6-ethylpyrimidine (1·0 g.) had m. p. 235°, undepressed in m. p. in admixture with an authentic specimen. From the neutralised alkaline liquors a quantity (1·1 g.) of unchanged starting material separated slowly.

(b) 5-p-*Chlorophenyl*-4-*ethyl*-2 : 6-*dimercaptopyrimidine*. The dimercaptopyrimidine (1·0 g.) and concentrated aqueous ammonia (20 ml.) were heated together at 155° in an autoclave overnight. The cooled suspension of colourless crystals was filtered and the solid (0·8 g.) was recrystallised twice from 2-ethoxyethanol, yielding 4-amino-5-*p*-chlorophenyl-6-ethyl-2-mercaptopyrimidine as colourless needles which blackened at 230—240° and had m. p. 326° (decomp.) (Found : C, 53·8; H, 4·7. Calc. for $C_{12}H_{12}N_3SCl$: C, 54·2; H, 4·5%). The ultraviolet light absorption of this compound was identical with that of the condensation product [12] of thiourea with 2-*p*-chlorophenyl-3-ethoxypent-2-enonitrile. Acidification of the ammonia

liquors with acetic acid yielded yellow crystals (0·2 g.), m. p. 215°. Recrystallised from benzene, this product had m. p. 235° and was identical with 2-amino-5-*p*-chlorophenyl-4-ethyl-6-mercaptopyrimidine.

2-*Amino*-5-p-*chlorophenyl*-4-*ethyl*-6-*methylthiopyrimidine* (XVI; R = NH_2, R′ = SMe).—A solution of 2-amino-5-*p*-chlorophenyl-4-ethyl-6-mercaptopyrimidine (1·3 g.) in methanol (20 ml.) containing 2N-sodium hydroxide (5 ml.) was treated with methyl iodide (1 ml.) and kept at room temperature overnight. Water was then added and the precipitated *methylthiopyrimidine* was collected and recrystallised from methanol, forming colourless prisms (1·2 g.), m. p. 196° (Found : C, 55·5; H, 5·0. $C_{13}H_{14}N_3SCl$ requires C, 55·8; H, 5·0%).

2-*Amino*-5-p-*chlorophenyl*-4-*ethylpyrimidine*.—The above methylthiopyrimidine (0·45 g.), ethanol (50 ml.), Raney nickel (2·0 g.), and sodium carbonate (0·3 g.) were heated together under reflux during 4 hr. The filtered solution was evaporated and the residual solid was crystallised from ether–light petroleum, yielding white needles of the *product*, m. p. 168° (Found : C, 61·9; H, 5·3. $C_{12}H_{12}N_3Cl$ requires C, 61·7; H, 5·15%). Its *picrate*, prepared in ethanol, crystallised from ethanol containing picric acid as yellow needles, m. p. 192—193° (Found : N, 18·5. $C_{12}H_{12}N_3Cl,C_6H_3O_7N_3$ requires N, 18·2%).

4-*Amino*-5-p-*chlorophenyl*-6-*ethyl*-2-*methylthiopyrimidine* (XVI; R = SMe, R′ = NH_2) was the product of reaction of 4-amino-5-*p*-chlorophenyl-6-ethyl-2-mercaptopyrimidine (0·5 g.) with methyl iodide in the manner described for the 2-amino-6-mercapto-analogue. Recrystallised from benzene–light petroleum, the methylthiopyrimidine (0·37 g.) had m. p. 156° (Found : C, 56·1; H, 5·3. $C_{13}H_{14}N_3SCl$ requires C, 55·8; H, 5·0%). By heating this compound (1·5 g.) with Raney nickel (5·0 g.) in ethanol (30 ml.), 4-amino-5-*p*-chlorophenyl-6-ethylpyrimidine was obtained; recrystallised from ethanol, and then from ether–light petroleum, it had m. p. 145° (Baker *et al.*[12] give m. p. 141—142°).

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