70. *Synthetic Antimalarials. Part III. Some Derivatives of Mono- and Di-alkylpyrimidines.*

By R. Hull, (Miss) B. J. Lovell, H. T. Openshaw, L. C. Payman, and A. R. Todd.

A series of simple pyrimidine derivatives bearing a variety of basic side chains has been prepared. A number of these show marked antiplasmodial action when tested against *P. gallinaceum* in chicks. The relation between chemical constitution and activity in these compounds is discussed and a hypothetical view of their mode of action advanced as a basis for further investigations.

In previous papers of this series (Curd and Rose, this vol., p. 343; Curd, Davis, and Rose, *ibid.* p. 351) an account has been given of some of the initial work on pyrimidines forming part of a general scheme directed to the synthesis of new chemotherapeutic agents for the treatment of malaria commenced in 1942 in the Research Department of Imperial Chemical Industries, Limited (Dyestuffs Division). Parallel with this work a cognate series of researches on pyrimidine derivatives was commenced in our laboratories as part of the same general scheme. It is a pleasure to record here our appreciation of a happy and fruitful collaboration, and it has seemed best to publish the results from both laboratories in the form of a single series of memoirs since the investigations are very closely related and impinge on each other at many points. All the biological tests here recorded were carried out in the Biological Department of Imperial Chemical Industries, Limited (Dyestuffs Division) by methods to be described in detail elsewhere.

The general considerations forming the basis of the chosen approach to the development of new antimalarial drugs have been described in Part I (Curd and Rose, *loc. cit.*). In our investigations we elected to study in the first instance pyrimidine derivatives bearing no aryl or arylamino substituents. Hitherto such simple derivatives had not, to our knowledge, been examined as antimalarials, although their omission in the course of

extensive research by many workers in the field seems rather surprising. Pyrimidine derivatives occupy positions of very great importance in the composition of living cells; they are, both as such and as the more complex purine derivatives, necessary components of the nucleic acids, and are integral parts of the molecules of a number of vitamins and biological oxidation–reduction catalysts (*e.g.*, aneurin, riboflavin, riboflavin-adenine-dinucleotide, coenzyme I and II) of fundamental importance to vital processes. Bearing in mind the view now generally held that certain chemotherapeutic agents (*e.g.*, sulphanilamide) exert their effect by a form of competition with some essential metabolic factor or co-enzyme (*e.g.*, *p*-aminobenzoic acid), it seemed not unreasonable to suppose that action of this type might be found among derivatives of pyrimidine.

A survey of the synthetic antimalarial drugs recorded in the literature (cf., *e.g.*, survey by Curd, *Ann. Trop. Med. Parasit.*, **1943**, **37**, 115; Bishop, *Parasitol.*, **1942**, **34**, 1) reveals the presence in most of those showing marked activity of dialkylaminoalkyl side chains attached to nitrogen. Whilst the significance of this grouping is not understood, it has been suggested that it may affect absorption and penetration of the drug (Magidson,

TABLE I.

Pyrimidine.	B. p. at $\sim 10^{-3}$ mm. (bath temp.).		Analysis, %. C.	H.	N.
4-*Amino*-6-β-*diethylaminoethylamino*-2-*methyl*	m. p. 109—110°	Found	59·9	9·2	31·1
		$C_{11}H_{21}N_5$ req.	59·2	9·4	31·4
4-*Amino*-6-γ-*diethylaminopropylamino*-2-*methyl*	m. p. 91—92·5°	Found	60·4	9·9	29·8
		$C_{12}H_{23}N_5$ req.	60·8	9·7	29·5
4-*Amino*-6-δ-*diethylamino*-α-*methylbutylamino*-2-*methyl*	170°	Found	63·3	9·9	25·7
		$C_{14}H_{27}N_5$ req.	63·4	10·2	26·4
4 : 6-*Bis*-(δ-*diethylamino*-α-*methylbutylamino*)-2-*methyl*	210°	Found	67·2	10·9	20·9
		$C_{23}H_{46}N_6$ req.	68·0	11·5	20·7
2-*Amino*-4-β-*diethylaminoethylamino*-6-*methyl*	161°/3 mm. (m. p. 70—72°)	Found	—	—	31·2
		$C_{11}H_{21}N_5$ req.	—	—	31·3
2-*Amino*-4-δ-*diethylamino*-α-*methylbutylamino*-6-*methyl*	170°	Found	63·0	10·4	26·6
		$C_{14}H_{27}N_5$ req.	63·4	10·2	26·4
2-*Piperidino*-4-δ-*diethylamino*-α-*methylbutylamino*-6-*methyl*	175°	Found	68·5	10·9	20·5
		$C_{19}H_{35}N_5$ req.	68·5	10·5	21·0
2 : 4-*Bis*-(δ-*diethylamino*-α-*methylbutylamino*)-6-*methyl*	170°	Found	67·6	10·9	20·1
		$C_{23}H_{46}N_6$ req.	68·1	11·3	20·6

Delektorskaya and Lipowitsch, *Arch. Pharm.*, **1934**, **272**, 74; Magidson and Grigorowsky, *Ber.*, **1936**, **69**, 396). It therefore seemed that, in our initial studies at any rate, it would be desirable to study pyrimidine derivatives bearing side chains of this type. It was also considered desirable to keep the molecule otherwise but lightly substituted, since interpretation of results was likely to be adversely affected by undue complication of the molecule. This paper records our results on a series of derivatives of mono- and di-alkylpyrimidines, and outlines some of the inferences which may be drawn and the directions on which further work (to be described later) is being developed. While it might have been considered more logical to commence our studies on pyrimidines bearing no alkyl substituents, the fact that they are more readily accessible led us to choose the mono- and di-alkylpyrimidines; moreover, the similar activity shown by sulphamezathine and sulphadiazine seemed to give additional justification for omitting the unsubstituted derivatives initially.

TABLE II.

4-*Substituted* 2 : 6-*Dimethylpyrimidines.*

Substituent.	B. p. at $<10^{-3}$ mm. (bath temp.).	Formula.	Found, %. C.	H.	N.	Required, %. C.	H.	N.
β-Diethylaminoethylamino	110°	$C_{12}H_{23}N_4$	64·2	10·1	24·9	64·9	9·9	25·2
δ-Diethylamino-α-methylbutylamino	130°	$C_{15}H_{28}N_4$	66·8	10·8	21·2	68·2	10·6	21·2
Piperidino	110° (*a*)	$C_{11}H_{17}N_3$	70·5	9·1	20·9	69·1	8·9	22·0
α-Pyridylamino	130°	$C_{11}H_{12}N_4$	66·5	5·9	27·3	66·0	6·0	28·0
*cyclo*Hexylamino	130° (*b*)	$C_{12}H_{19}N_3$	69·3	9·0	19·7	70·3	9·2	20·5
Diethylamino	85°	$C_{10}H_{17}N_3$	67·1	9·4	23·7	67·1	9·5	23·4

(*a*) 3 : 5-*Dinitrobenzoate*, fluffy needles from alcohol, m. p. 151° (Found: C, 49·2; H, 4·2; N, 16·5. $C_{11}H_{17}N_3,2C_7H_4O_6N_2$ requires C, 48·8; H, 4·1; N, 15·9%).

(*b*) *Flavianate*, yellow leaflets from alcohol, m. p. 190° (decomp.) (Found: C, 50·9; H, 5·0; N, 13·6. $C_{12}H_{19}N_3,C_{10}H_6O_8N_2S$ requires C, 50·9; H, 4·8; N, 13·5%).

Our studies commenced with the preparation of a number of *derivatives* (Table I) of 2- and 6-methylpyrimidine containing basic groups; none of these showed any activity when tested against *P. gallinaceum* in chicks. Similar lack of antimalarial activity was encountered in the series of *derivatives* of 2 : 6-dimethylpyrimidine bearing a basic substituent in position 4 (Table II). Only one derivative of 4 : 6-dimethylpyrimidine, *viz.*, 2-(δ-*diethylamino*-α-*methylbutylamino*)-4 : 6-*dimethylpyrimidine*, was examined; it, too, was inactive against *P. gallinaceum*. Antimalarial activity was first encountered when basic side chains were introduced at position 4 in 2-amino-5 : 6-dimethylpyrimidine. Thus 2-*amino*-4-(δ-*diethylamino*-α-*methyl*-

butylamino)-5 : 6-*dimethylpyrimidine* (I; R = CHMe·$[CH_2]_3$·NEt_2) and 2-*amino*-4-*γ*-*diethylaminopropylamino*-5 : 6-*dimethylpyrimidine* (I; R = $[CH_2]_3$·NEt_2) were highly active against *P. gallinaceum* in chicks at a dose of 4 mg./50 g. although they were rather toxic to the host (*e.g.*, maximum tolerated dose of (I; R = $[CH_2]_3$·NEt_2), 4 mg./50 g.; MLD (mice) orally, 250—500 mg./kg.).

Omission of the 2-amino-group giving compounds of Type (II) or its replacement by methyl (Type III) reduced the activity very markedly without materially affecting the toxicity of the compounds; replacement of the 2-amino-group by a second dialkylaminoalkyl group (Type IV) appeared to destroy the antimalarial activity. These findings led naturally to a study of the effect of varying the nature of the basic side chain and the alkyl groups at C_5 and C_6. The *compounds* prepared are listed in Tables III and IV; none showed an

TABLE III.

4-Substituted 2-Amino-5 : 6-Dimethylpyrimidines.

Substituent.	B. p. at ~10^{-3} mm. (bath temp.).	M. p.	Formula.	Found, %. C.	H.	N.	Required, %. C.	H.	N.	Antimalarial activity. Dose, mg./kg.	Activity.
NEt_2	100°/15 mm.	66—68° (*a*)	$C_{10}H_{18}N_4$	61·9	8·9	28·7	61·9	9·3	28·8	50	–
NH·$[CH_2]_2$·NEt_2	135°	67—72°	$C_{12}H_{23}N_5$	61·3	10·1	29·2	60·8	9·7	29·5	100	++
NH·$[CH_2]_3$·NEt_2	180—190°	107—108° (*b*)	$C_{13}H_{25}N_5$	62·0	9·7	28·0	62·1	10·0	27·9	80	++
										40	±
NH·$[CH_2]_4$·NEt_2	175—180°	58—61°	$C_{14}H_{27}N_5$	63·4	9·9	26·4	63·3	10·3	26·4	80	++
										40	±
NH·CHMe·$[CH_2]_3$·NEt_2	140°	82—83°	$C_{15}H_{29}N_5$	64·5	10·4	25·1	64·4	10·2	25·0	100	++
										50	–
NH·$[CH_2]_2$·NMe_2	150—155°	(*c*)	$C_{10}H_{19}N_5$	57·5	9·3	33·5	57·4	9·2	33·5	80	+
										40	–
NH·$[CH_2]_3$·NMe_2	155—165°	75—76°	$C_{11}H_{21}N_5$	58·9	9·4	31·8	59·1	9·5	31·4	80	+
										40	–
NH·$[CH_2]_2$·NHBu^a	165—170°	91—94°	$C_{12}H_{25}N_5$	62·5	10·0	27·6	62·1	10·0	27·9	20	toxic
NH·$[CH_2]_2$·NBu^a_2	190°/0·25 mm.	(*d*)	$C_{17}H_{33}N_5$	65·8	10·7	23·1	66·4	10·8	22·8	20	toxic
NH·$[CH_2]_2$·NC_5H_{10}	170°	145·5—146·5° (*b*)	$C_{14}H_{25}N_5$	63·6	9·4	26·9	63·8	9·6	26·6	80	++
										40	+
NH·$[CH_2]_2$·NMe·$[CH_2]_2$·NEt_2	220—230°	41—43° (*e*)	$C_{16}H_{32}N_6$	61·6	10·1	27·5	62·3	10·4	27·3	80	++
										40	–
NH·$[CH_2]_2$·O·$[CH_2]_2$·NEt_2	210—220°	(*f*)	$C_{18}H_{29}ON_5$	60·0	10·3	24·5	61·0	9·9	23·7	80	–
NH·$[CH_2]_2$·NH_2	subl. 150—160°	160·5—161·5°	$C_9H_{15}N_5$	52·9	7·9	38·7	53·0	8·3	38·7	320	–
NMe·$[CH_2]_2$·NEt_2	170—180°	(*g*)	$C_{13}H_{25}N_5$	61·4	9·8	27·9	62·1	10·0	27·9	80	++
										40	+

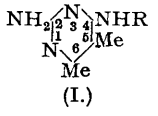
(*a*) Recrystallised from light petroleum. (*b*) Recrystallised from benzene. (*c*) Softens at 90°, clears at 123°.
(*d*) 3 : 5-*Dinitrobenzoate*, m. p. 194—195° (decomp.) (Found: C, 50·9; H, 5·9; N, 17·1. $C_{17}H_{32}N_5,2C_7H_4O_6N_2$ requires C, 50·9; H, 5·6; N, 17·2%).
(*e*) Recrystallised from light petroleum. Very hygroscopic.
(*f*) 3 : 5-*Dinitrobenzoate*, m. p. 210° (decomp.) (Found: C, 48·7; H, 5·2; N 17·7. $C_{18}H_{29}ON_5,2C_7H_4O_6N_2$ requires C, 48·4; H, 5·2; N, 17·5%).
(*g*) 3 : 5-*Dinitrobenzoate*, m. p. 154—156° (Found: C, 47·6; H, 5·4; N, 19·1. $C_{13}H_{25}N_5,2C_7H_4O_6N_2$ requires C, 48·0; H, 4·9; N, 18·7%).

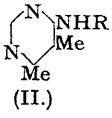
TABLE IV.

Variation of Alkyl Substituents in 2-Amino-4-dialkylaminoalkylamino-5 : 6-dialkylpyrimidines.

Substituents, at positions 5 and 6.	at position 4.	M. p.	Formula.	Found, %. C.	H.	N.	Required, %. C.	H.	N.	Antimalarial activity. Dose, mg./kg.	Activity.
5-Ethyl-6-methyl	NH·$[CH_2]_2$·NEt_2	86°	$C_{12}H_{24}N_5$	—	—	27·6	—	—	27·9	80	+
										40	–
,,	NH·CHMe·$[CH_2]_3$·NEt_2	91—93°	$C_{16}H_{31}N_5$	65·0	10·7	23·4	65·0	10·6	23·9	100	+
5-Benzyl-6-methyl	NH·$[CH_2]_2$·NEt_2	123·5—125°	$C_{18}H_{27}N_5$	69·0	8·6	22·3	69·0	8·6	22·4	80	–
,,	NH·$[CH_2]_2$·NEt_2	126·5°	$C_{19}H_{29}N_5$	69·9	8·5	21·1	69·7	8·9	21·4	80	++
										40	±
,,	NH·CHMe·$[CH_2]_3$·NEt_2	—	$C_{21}H_{33}N_5$	71·2	8·7	20·2	71·0	9·3	19·7	80	±
5 : 6-*cyclo*Hexeno-	NH·$[CH_2]_2$·NEt_2	117—118°	$C_{14}H_{25}N_5$	64·0	9·6	26·4	63·9	9·5	26·6	80	++
										40	±
,,	NH·$[CH_2]_3$·NEt_2	87—90°	$C_{15}H_{27}N_5$	64·9	9·8	24·9	65·0	9·7	25·3	80	+
,,	NH·CHMe·$[CH_2]_3$·NEt_2	112·5—113°	$C_{17}H_{31}N_5$	67·0	10·2	22·4	66·9	10·2	22·9	80	toxic
										40	–
5 : 6-*cyclo*Penteno-	NH·$[CH_2]_2$·NEt_2	83—84°	$C_{13}H_{23}N_5$	62·3	9·1	28·7	62·6	9·2	28·1	120	toxic
										80	–
,,	NH·$[CH_2]_3$·NEt_2	84·5—85·5°	$C_{14}H_{25}N_5$	63·9	9·6	26·2	63·9	9·5	26·6	80	–
,,	NH·CHMe·$[CH_2]_3$·NEt_2	118—119°	$C_{15}H_{29}N_5$	65·9	9·9	23·7	66·0	10·0	24·0	40	–

appreciably higher antimalarial activity than the two compounds of Type I first prepared, and many showed an increased toxicity.


(I.)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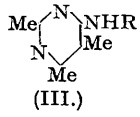
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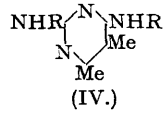
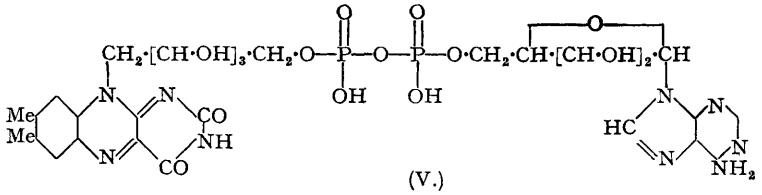

(IV.)

It was now clear that our original hope that antimalarial activity might be found in comparatively simple pyrimidine derivatives had been realised irrespective of the validity of the considerations which had led us to embark on their synthesis, but it was necessary to examine the position more closely in order to establish a *rationale* for further development of our investigations. An obvious step was to consider whether the active substances might exert their effects by interference with some known essential enzyme system in the malarial

parasite. It has been shown by Madinaveitia (*Biochem. J.*, in press) using *Lactobacillus casei* as a test organism that the growth-inhibitory action of a number of the known antimalarial drugs, *e.g.*, mepacrine, quinine, and the 2-arylaminopyrimidine derivatives described by Curd and Rose (Part I, *loc. cit.*), is antagonised by riboflavin. This has led not unnaturally to the view that the action of these drugs may be due to some kind of interference with the functioning of riboflavin-containing enzymes in the malaria parasite. It is true that little or nothing is known of the nutritional requirements of the malaria parasite, but it is reasonable to assume, in view of their universal occurrence, that riboflavin-containing enzymes are concerned in their metabolism. Dr. Madinaveitia has examined our active compound (I; R = $CHMe\cdot[CH_2]_3\cdot NEt_2$) in the *L. casei* test and has found that, unlike the other antimalarials mentioned, there is no evidence of antagonism by riboflavin.

Perhaps the commonest known derivative of riboflavin exerting co-enzyme function is riboflavin-adenine-dinucleotide believed to possess structure (V). This compound is associated with specific proteins in a number of enzyme systems vital to cell metabolism, and interference with its synthesis or with its combination with the appropriate proteins in the parasites might well explain the action of an antimalarial drug. That a riboflavin antagonist such as mepacrine might interfere in either or both of these ways is clear, but it is equally clear that interference might, in other agents, rest on the adenosine rather than the riboflavin portion of the molecule. When one considers interference of the latter type it is evident that the number of possibilities is increased by the fact that nucleoside synthesis is a general property of cells; it may indeed be possible to hinder the synthesis of riboflavin-adenine-dinucleotide by interfering with the synthesis of adenosine. Such an interference might, of course, similarly affect other co-enzymes, *e.g.*, the co-dehydrases, adenosine triphosphate, etc. Interference with nucleoside synthesis does in fact seem to us to be a probable mode of action of the simple pyrimidines we are investigating. This view rests on the following, admittedly speculative, reasoning.



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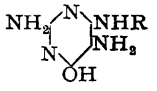

(VI.)

Examination of the structural formulæ of riboflavin and the purine nucleosides reveals a striking similarity in the location of the carbohydrate residue relative to the pyrimidine nucleus. This similarity, already noted by others (cf., *e.g.*, Hirst, *Ann. Reports*, 1936, **33**, 254), can hardly be fortuitous and probably indicates a biogenetic relationship. In investigations on purine nucleosides in these laboratories 9-glycosidopurine derivatives have been synthesised from 5-amino-4-glycosidaminopyrimidines by thioformylation and subsequent cyclisation (cf., *e.g.*, Baddiley, Lythgoe, and Todd, *J.*, 1944, 318). We consider it not impossible that such 5-amino-4-glycosidaminopyrimidines are intermediates in the biogenesis both of nucleosides and of riboflavin. Condensation of (VI; R = *d*-ribosido), for example, with formic acid might yield guanosine, while a simple conversion to the corresponding 4-*d*-ribitylamino compound—possibly by way of an Amadori rearrangement—followed by condensation with 1 : 2-dihydroxy-4 : 5-dimethylbenzene or some suitable derivative followed by deamination would yield riboflavin or its dihydro-derivative. There is as yet no laboratory analogy for a riboflavin synthesis on these lines, although it bears an obvious analogy to the synthesis of alloxazines from 5 : 6-diaminopyrimidine and the synthesis of phenazine from catechol and *o*-phenylenediamine (Merz, *Ber.*, 1886, **19**, 725).

Accepting the feasibility of this scheme of biogenesis it would be expected that pyrimidine derivatives substituted in the 4 : 5-positions and in particular those bearing a side-chain of moderate size in position 4 might interfere with nucleoside (and possibly riboflavin) synthesis. It is a fact that of the compounds described in this paper only those fulfilling these conditions show antimalarial activity. It may also be significant that this action is associated with rather high toxicity; clearly a drug interfering with nucleoside synthesis might have a powerful toxic action on host as well as parasite.

These views may or may not be valid, but they have been accepted by us as a working hypothesis for further investigations now in progress. These include the synthesis of a variety of other pyrimidines substituted in position 5 which might be expected to block purine synthesis, as well as of purine derivatives which might block the subsequent co-enzyme syntheses. These studies will be reported in due course, but it may be mentioned here that, whatever the validity of our hypothesis, they have already led to the discovery of further compounds showing marked antimalarial activity.

The dialkylaminoalkylamino-pyrimidines described in this paper are all new and have been prepared from the corresponding chloropyrimidines by reaction with an excess of the appropriate amine. The majority of the chloropyrimidines and intermediates used in their preparation have already been described, but several are new and others have been prepared by methods differing from those in the literature.

4-Hydroxy-5 : 6-dimethylpyrimidine was prepared by condensation of formamidine with ethyl α-methylacetoacetate; this compound has been prepared by Schlenker (*Ber.*, 1901, **34**, 2824) by heating 2 : 4-dichloro-5 : 6-dimethylpyrimidine with hydriodic acid and red phosphorus. 4-Amino-6-hydroxy-2-methylpyrimidine was readily obtained by interaction of equimolecular amounts of acetamidine, ethyl cyanoacetate, and sodium ethoxide (Traube, *Centr.*, 1902, II, 1229): omission of the sodium ethoxide led to formation of a product believed

to be *ethyl* β-*amino*-α-*cyanocrotonate* (cf. Kenner, Lythgoe, Todd, and Topham, *J.*, 1943, 388). 2-*Piperidino*-4-*hydroxy*-6-*methylpyrimidine* was obtained in good yield by heating 4-hydroxy-2-ethylthio-6-methylpyrimidine with excess of piperidine, and was converted into the 4-*chloro*-derivative by heating with phosphoryl chloride. 2 : 4-Dihydroxy-5 : 6-dimethylpyrimidine necessary for the preparation of the corresponding dichloro-compound was conveniently prepared by heating 4-*hydroxy*-2-*thiol*-5 : 6-*dimethylpyrimidine* with aqueous chloroacetic acid. 2-*Amino*-4-*hydroxy*-5-*benzyl*-6-*methylpyrimidine* was prepared by condensation of guanidine with ethyl α-benzylacetoacetate, and converted into the 4-*chloro*-compound by the action of phosphoryl chloride. 2-Amino-4-hydroxy-5 : 6-*cyclo*hexenopyrimidine (Mitter and Bhattacharya, *Quart. J. Ind. Chem. Soc.*, 1927, **4**, 149) and 2-*amino*-4-*hydroxy*-5 : 6-cyclo*pentenopyrimidine* were similarly obtained from guanidine and the appropriate β-keto-esters, and were converted into the corresponding 4-chloro-compounds in the usual way.

Experimental.

Condensation of Acetamidine with Ethyl Cyanoacetate.—To an ice-cold solution of sodium (8·3 g. ≡ 1 atom) in ethanol (200 c.c.), acetamidine hydrochloride (33·8 g. ≡ 1 mol.) was added, followed by ethyl cyanoacetate (41 g. ≡ 1 mol.). After leaving overnight at room temperature, the mixture was heated under reflux for 2 hours, and filtered from sodium chloride. After removal of a portion of the alcohol by distillation, the solution was cooled, and the product (20·6 g.; 37%) collected by filtration, washed, and recrystallised from alcohol. *Ethyl* β-*amino*-α-*cyanocrotonate* formed colourless prisms, m. p. 190° (Found: N, 17·9. $C_7H_{10}O_2N_2$ requires N, 18·2%).

2-*Piperidino*-4-*hydroxy*-6-*methylpyrimidine.*—A solution of 4-hydroxy-2-ethylthio-6-methylpyrimidine (20 g.) (Johns, *Amer. Chem. J.*, 1908, **40**, 350) in piperidine (100 c.c.) was refluxed for 8 hours; evolution of ethylthiol occurred. Excess of piperidine was removed by distillation under reduced pressure and the brownish residue crystallised from ethyl acetate; 2-*piperidino*-4-*hydroxy*-6-*methylpyrimidine* (17·5 g.; 72%), m. p. 180—184°, was obtained. Two recrystallisations from methanol–ethyl acetate (charcoal) afforded colourless needles, m. p. 185° (Found: C, 62·0; H, 7·6. $C_{10}H_{15}ON_3$ requires C, 62·2; H, 7·8%).

4-*Chloro*-2-*piperidino*-6-*methylpyrimidine.*—The above hydroxy-compound (8·5 g.) was heated under reflux with phosphoryl chloride (50 c.c.) for 4 hours; excess of reagent was removed by distillation under reduced pressure, and the residual oil was decomposed with ice. The resulting solution was made alkaline with ammonia and extracted with ether. After drying over sodium sulphate, the extract was distilled, 4-chloro-2-piperidino-6-methylpyrimidine (5·7 g.; 61%) being collected at 292—293° as a yellow oil. The *picrate*, recrystallised from 80% alcohol, had m. p. 98·5—99·5° (Found: C, 44·2; H, 4·1; N, 18·7. $C_{10}H_{14}N_3Cl,C_6H_3O_7N_3$ requires C, 43·5; H, 3·9; N, 19·0%).

4-*Hydroxy*-5 : 6-*dimethylpyrimidine.*—Formamidine hydrochloride (16·1 g.) was added to ice-cold alcoholic sodium ethoxide (from 4·6 g. of sodium and 200 c.c. of alcohol), and the mixture was shaken for 10 minutes. The resulting solution of formamidine was treated with ethyl α-methylacetoacetate (28·8 g.), and, after leaving for 3 days at room temperature, it was filtered from sodium chloride and evaporated to dryness. 4-Hydroxy-5 : 6-dimethylpyrimidine (6·0 g.; 24%) remained as a colourless solid, m. p. 202—204° (Schlenker, *loc. cit.*, gives m. p. 204°). A specimen was recrystallised from alcohol for analysis (Found: C, 57·5; H, 6·5. Calc. for $C_6H_8ON_2$: C, 58·0; H, 6·4%).

4-*Chloro*-5 : 6-*dimethylpyrimidine.*—A solution of the crude hydroxydimethylpyrimidine (6 g.) in phosphoryl chloride (36 c.c.) was heated under reflux for 3 hours, and excess of phosphoryl chloride was removed under reduced pressure. The residue was added to ice, and the resulting solution made alkaline with aqueous ammonia and extracted with ether. The extract was dried and distilled; the chloro-compound (4·1 g.; 60%) boiled at 206° and was a yellow liquid of unpleasant " mousy " odour which solidified on cooling and then had m. p. 48° (Schlenker, *loc. cit.*, gives m. p. 51°).

4-*Hydroxy*-2-*thiol*-5 : 6-*dimethylpyrimidine.*—Thiourea (38 g.) and ethyl α-methylacetoacetate (72 g.) were added to alcoholic sodium ethoxide (from 11·5 g. of sodium and 200 c.c. of alcohol), and the solution heated under reflux for 2 hours. Alcohol was removed by evaporation and the residual sodium salt was dissolved in water; the filtered solution was acidified with hydrochloric acid, and the precipitated 4-*hydroxy*-2-*thiol*-5 : 6-*dimethylpyrimidine* (34 g.) was collected, washed with water, and dried. It crystallised from hot water as colourless needles, m. p. 278—280° (decomp.) (Found: C, 46·7; H, 5·3; N, 17·7. $C_6H_8ON_2S$ requires C, 46·2; H, 5·1; N, 17·9%).

2 : 4-*Dihydroxy*-5 : 6-*dimethylpyrimidine.*—The above thiol (34 g.) was heated under reflux for 8 hours with a solution of chloroacetic acid (34 g.) in water (2 l.). On cooling the hot, filtered solution, the dihydroxy-compound separated as colourless needles, m. p. 294—297° (decomp.) (22 g.; 78%). Behrend and Kircher (*Annalen*, 1911, **385**, 305) give m. p. 294—296° (decomp.).

4-*Chloro*-2 : 5 : 6-*trimethylpyrimidine.*—A mixture of 4-hydroxy-2 : 5 : 6-trimethylpyrimidine (Pinner, *Ber.*, 1889, **22**, 1617) (10·5 g.) and phosphoryl chloride (60 c.c.) was heated under reflux for 4 hours, and the product was isolated in the usual manner. 4-Chloro-2 : 5 : 6-trimethylpyrimidine (8·2 g.; 69·5%) had b. p. 215°, and was a yellow liquid of characteristic " mousy " odour. The *picrate* had m. p. 132° (Found: C, 40·5; H, 3·1; N, 18·1. $C_7H_9N_2Cl,C_6H_3O_7N_3$ requires C, 40·5; H, 3·1; N, 18·2%).

2-*Amino*-4-*hydroxy*-5-*benzyl*-6-*methylpyrimidine.*—Guanidine hydrochloride (57·3 g.) was added to alcoholic sodium ethoxide (from 13·8 g. of sodium and 325 c.c. of alcohol), and the mixture was shaken vigorously for 5 minutes. Ethyl α-benzylacetoacetate (132 g.) was now added and the mixture, after keeping overnight, was heated under reflux for 2 hours. The solid material was collected from the cooled mixture and stirred with cold water (200 c.c.). It was again collected, washed free from sodium chloride, and dried, first at 40°, then at 100°. The colourless, crystalline *product* (84 g.; 65%), m. p. 273—275°, was used without further purification. Recrystallisation of a specimen from water raised the m. p. to 277·5—278·5° (Found: C, 66·7; H, 6·2; N, 19·5. $C_{12}H_{13}ON_3$ requires C, 67·0; H, 6·1; N, 19·6%).

4-*Chloro*-2-*amino*-5-*benzyl*-6-*methylpyrimidine.*—The above hydroxy-compound (55 g.) was treated with phosphoryl chloride in the usual manner. After pouring the crude product on ice, the solution obtained was made alkaline with ammonia, keeping the temperature below 25°. The *chloro*-compound separated as a solid, which was collected, washed with cold water, and dried at 40°. On crystallisation from alcohol (charcoal), the substance (25 g.; 42%) was obtained as a colourless, microcrystalline powder, m. p. 182·5—183·5°. Further recrystallisation raised the m. p. to 184·5—185·5° (Found: C, 61·4; H, 5·3; N, 17·9. $C_{12}H_{12}N_3Cl$ requires C, 61·7; H, 5·1; N, 18·0%).

2-*Amino*-4-*hydroxy*-5 : 6-cyclo*hexenopyrimidine* (cf. Mitter and Bhattacharya, *loc. cit.*).—Guanidine hydrochloride (76·4 g.) was added to warm alcoholic sodium ethoxide (from 18·4 g. of sodium and 432 c.c. of alcohol), and the mixture was allowed to stand for 10 minutes with occasional shaking. Ethyl *cyclo*hexanone-2-carboxylate (136 g.) was added and, after leaving overnight, the mixture was heated under reflux for 2 hours. The colourless, solid material was collected, washed by stirring with cold water (1 l.) and again collected by filtration. After further washing on the filter, the product (120 g.; 91%) was dried at 100°. On crystallisation from hot water it formed colourless prisms, m. p. >300° (Found: C, 58·2; H, 6·6; N, 25·6. Calc. for $C_8H_{11}ON_3$: C, 58·2; H, 6·6; N, 25·5%).

2-*Amino*-4-*hydroxy*-5 : 6-cyclo*pentenopyrimidine* was obtained from ethyl *cyclo*pentanone-2-carboxylate (125 g.) in an analogous manner. The colourless *product* (75·5 g.; 62·5%) did not melt below 300°; it crystallised from hot water in prisms (Found: C, 55·8; H, 6·1; N, 27·7. $C_7H_9ON_3$ requires C, 55·6; H, 6·0; N, 27·8%).

4-*Chloro*-2-*amino*-5 : 6-cyclo*hexenopyrimidine*.—The hydroxy-compound (57·8 g.) was heated under reflux with phosphoryl chloride (250 c.c.) until a clear solution was obtained (*ca.* 30 minutes); excess of reagent was removed under reduced pressure and the product was isolated in the usual manner; the *chloro*-compound (55 g.; 85%) was thus obtained as a colourless, crystalline solid, m. p. 202—203°; it was soluble in benzene, acetone, and alcohol, but very sparingly soluble in hot water. Crystallisation from alcohol afforded colourless needles, m. p. 206—207° (Found: C, 51·9; H, 5·5; N, 23·3. $C_8H_{10}N_3Cl$ requires C, 52·3; H, 5·5; N, 22·9%).

4-*Chloro*-2-*amino*-5 : 6-cyclo*pentenopyrimidine*, prepared similarly, and crystallised from alcohol, had m. p. 197—198° (Found: C, 50·0; H, 4·9; N, 24·8. $C_7H_8N_3Cl$ requires C, 49·6; H, 4·7; N, 24·8%).

Alkylaminopyrimidines.—The compounds listed in Tables I, II, III, and IV were prepared by the following general method. The chloropyrimidine (4—7 g.) was dissolved in about 5 times its weight of the appropriate amine and the solution refluxed for 4—6 hours; the method was slightly varied for the 4-diethylamino-compounds where, for obvious reasons, the heating with diethylamine was carried out in a sealed tube at 150—160°. Excess of amine was then removed by distillation under reduced pressure from an oil-bath, and the residue dissolved in the minimum quantity of dilute hydrochloric acid. The product was liberated by addition of excess of solid sodium hydroxide. Rarely, the crude product was a solid which could be purified by crystallisation; usually it formed a viscous oil, which was extracted with ether. The ethereal solution was dried over sodium sulphate and evaporated, and the residue was distilled at *ca.* 10^{-3} mm. from a metal-bath. Many of the distilled products crystallised on standing, or on trituration with cold, anhydrous ether; they were then further purified by recrystallisation from light petroleum, benzene–petroleum, or aqueous alcohol. Those which did not crystallise were redistilled in a high vacuum; they were usually highly viscous and light yellow. The crystalline products were all colourless. The yields usually ranged from 70 to 90%, depending mainly on the losses involved in purification.

In addition to the substances listed in Tables I—IV, the following were prepared by the same general method. 2-δ-*Diethylamino*-α-*methylbutylamino*-4 : 6-*dimethylpyridine* distilled at 10^{-4} mm. at 130° (bath temp.) as a pale yellow oil (74%) (Found: C, 67·7; H, 10·9; N, 20·7. $C_{15}H_{28}N_4$ requires C, 68·2; H, 10·6; N, 21·2%). 4-δ-*Diethylamino*-α-*methylbutylamino*-5 : 6-*dimethylpyrimidine*, after two successive distillations at 135—140° (bath temp.), set to a waxy, hygroscopic solid (71%), m. p. 48—49°. A specimen was distilled a third time for analysis (Found: C, 67·5; H, 10·4; N, 19·9. $C_{15}H_{28}N_4$ requires C, 68·2; H, 10·6; N, 21·2%). 4-δ-*Diethylamino*-α-*methylbutylamino*-2 : 5 : 6-*trimethylpyrimidine* distilled at 130° (bath temp.) as a viscous, straw-coloured oil (74%) (Found: C, 68·7; H, 10·7; N, 19·8. $C_{16}H_{30}N_4$ requires C, 69·1; H, 10·8; N, 20·1%). 2 : 4-*Bis*-(δ-*diethylamino*-α-*methylbutylamino*)-5 : 6-*dimethylpyrimidine*, b. p. 160°/10^{-4} mm. (bath temp.), was a yellowish-brown oil (74%) (Found: C, 68·4; H, 11·2; N, 19·8. $C_{24}H_{48}N_6$ requires C, 68·6; H, 11·4; N, 20·0%).

The following Experiments were carried out by Dr. R. De B. Ashworth, I.C.I. Ltd. (*Dyestuffs Division*).—2-*Amino*-4-β-*diethylaminoethylamino*-6-*methylpyrimidine*. 4-Chloro-2-amino-6-methylpyrimidine (43 g.; Gabriel and Colman, *Ber.*, 1899, **32**, 2924) was added to a mixture of β-diethylaminoethylamine (52 g.) and glacial acetic acid (52 c.c.). After heating on a water-bath for 3 hours the clear solution was poured into water (500 c.c.), the solution filtered, and sodium hydroxide solution (200 c.c. of 34%) added followed by solid sodium hydroxide (100 g.). The precipitated oil was separated, the aqueous layer extracted with benzene, and the benzene extract added to the oil. After drying for several days over solid sodium hydroxide and then removing the benzene by evaporation, the product was distilled in a vacuum using a short electrically heated Vigreux column and the fraction b. p. 161°/3 mm. collected. 2-*Amino*-4-β-*diethylaminoethylamino*-6-*methylpyrimidine* (45·6 g.; 68·3%) thus obtained formed a slightly yellow oil which gradually solidified on standing and was then crystallised from ligroin (b. p. 60—80°); it had m. p. 70—72° (Found: N, 31·2. $C_{11}H_{21}N_5$ requires N, 31·3%). The *dipicrate* formed yellow crystals, m. p. 216—218°, by crystallisation from acetone–alcohol (Found: C, 40·8; H, 4·2; N, 22·3. $C_{11}H_{21}N_5,2C_6H_3O_7N_3$ requires C, 40·5; H, 4·0; N, 22·6%).

2-*Amino*-4-β-*diethylaminoethylamino*-6-*methyl*-5-*ethylpyrimidine*. A mixture of 4-chloro-2-amino-6-methyl-5-ethylpyrimidine (51 g.; Byk, *Ber.*, 1905, **36**, 1915), β-diethylaminoethylamine (52 g.), and glacial acetic acid (52 c.c.) was heated on a water-bath for 3 hours and then refluxed for ¼ hour. The homogeneous mixture was poured into a large excess of water and filtered from some 2-amino-4-hydroxy-6-methyl-5-ethylpyrimidine. The filtrate was added to excess of 34% sodium hydroxide solution, the precipitated oil separated, and the aqueous layer extracted with benzene. The oily layer and the benzene extract were combined, dried over solid sodium hydroxide, and evaporated. The residual oil was distilled in a vacuum using a short electrically heated bead column, and the fraction of b. p. 210°/6 mm. collected (yield, 58·5%). By crystallisation from ligroin (b. p. 60—80°) 2-*amino*-4-β-*diethylaminoethylamino*-6-*methyl*-5-*ethylpyrimidine* was obtained as clusters of colourless needles, m. p. 86° (Found: N, 27·6. $C_{13}H_{25}N_5$ requires N, 27·9%).

THE UNIVERSITY, MANCHESTER.

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