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5-HALOGENOPYRIMIDINES—IV*†

EXTENSION ON THE NATURE OF PYRIMIDINE SUBSTRATES AND THE KIND OF N-HALOGENOSUCCINIMIDES

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Abstract—The preparation of 5-halogenopyrimidines with N-halogenosuccinimide has been examined. The reaction of pyrimidines with N-chlorosuccinimide or N-bromosuccinimide yields 5-chloro- or 5-bromopyrimidines, if one amino (primary or secondary), one hydroxy, or two alkoxy groups are present at the 2-, 4-, or 6-positions. The presence of one alkoxy group in addition to other substituents was not effective for these chlorination or brominations. Iodination by N-iodosuccinimide was also attempted, but in most aminopyrimidines instability of 5-iodopyrimidines complicated the results. The UV absorptions of 5-halogenopyrimidines are recorded. The halogen atom at the 5-position generally causes a bathochromic shift.

5-HALOGENOPYRIMIDINES,[1] an interesting class of compounds biologically as well as chemically, have been prepared by the direct halogenation of pyrimidines. This method is good if one or more electron-donating substituents are present at the 2-, 4-, and 6-positions because of the enhanced availability of electrons at the 5-position, which otherwise are depleted by the electrophilic ring nitrogen atoms. The reagents of choice for this direct halogenations are free halogens, iodine monochloride,[2] sodium hypobromite,[3] dioxan dibromide,[4] and hydrochloric acid in the presence of hydrogen peroxide.[5]

Aliphatic compounds containing a halogen atom such as ethyl formylchloroacetate,[6] ethyl fluoroacetate,[7] or ethyl bromocyanoacetate[8] have also been used in the synthesis of 5-halogenopyrimidines.

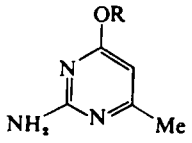
Several years ago the successful bromination of pyrimidines with N-bromosuccinimide (NBS)[9–11] was reported. Renewed chemical[12] and continued biological[13]

* Ref. 11 is considered to be Part III of this series.

For convenience all compounds are named as hydroxy, or amino derivatives whatever their keto forms may exist.

[1] For the review of halogenopyrimidines see D. Brown, *The Pyrimidines* p. 162. Interscience, New York (1962).
[2] D. Brown, *J. Soc. Chem. Ind.* **69**, 353 (1950).
[3] O. Stark, *Liebigs Ann.* **381**, 143 (1911).
[4] J. Filips and J. Moravek, *Chem. & Ind.* 260 (1960).
[5] T. Johnson, *J. Amer. Chem. Soc.* **65**, 1218 (1943).
[6] Z. Budesinsky, V. Jelinek and J. Prikryl, *Coll. Czech. Chem. Comm.* **27**, 2550 (1962).
[7] R. Duschinsky, E. Pleven and C. Heidelberger, *J. Amer. Chem. Soc.* **79**, 4559 (1957).
[8] A. Bendich and G. Clements, *Biochim. et Biophys. Acta* **12**, 462 (1953).
[9] T. Nishiwaki, *Bull. Chem. Soc. Japan* **33**, 26 (1960).
[10] T. Nishiwaki, *Chem. and Pharm. Bull.* **9**, 38 (1961).
[11] T. Nishiwaki, *Chem. and Pharm. Bull.* **10**, 1029 (1962).
[12] T. Kauffmann, *Angew. Chem.* **77**, 557 (1965).
[13] W. Razzell and P. Casshyap, *J. Biol. Chem.* **239**, 1789 (1964).

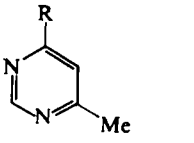
interest on 5-halogenopyrimidines warrants an extension both in the nature of pyrimidine substrates and the kind of N-halogenosuccinimides, such as N-chlorosuccinimide (NCS) and N-iodosuccinimide (NIS). As to the 5-iodopyrimidines, Lipkin, *et al.*[14] obtained 5-iodouridine triphosphate by the action of NIS on uridine triphosphate.



I R = Me

II R = Et

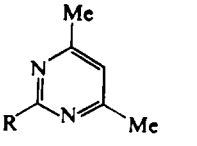
III R = C_6H_4Cl-*p*



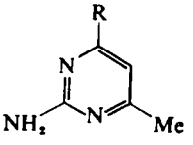
IV R = NHC_6H_4Cl-*p*

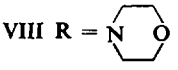
X R = NH_2

XVII R = OH



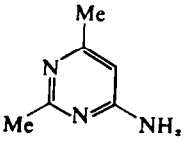
VII R = n-BuNH
XV R = OEt
XVI R = OH



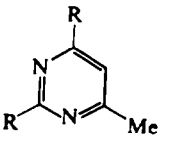


VIII R =

IX R = NHC_6H_4Cl-*p*
XI R = OH
XII R = Me
XIII R = Cl



XIV



XVIII R = OMe

XIX R = OH

Unknown 5-unsubstituted pyrimidines (I-VI) required for the present study were prepared by conventional procedures.

Bromination by NBS, or chlorination by NCS, of monoaminopyrimidines, such as 2-amino-4-alkoxy (or phenoxy)-6-methyl-, 2-amino-4-morpholino-6-methyl- and 2-amino-4-*p*-chloroanilino-6-methylpyrimidines (I, II, III, VIII, and IX) yielded the corresponding 5-bromo- or 5-chloro- pyrimidines in excellent yield. The 5-chloropyrimidines were inclined to sublime over 100°, and this may account for the lower yield of 4-amino-5-chloro-6-methylpyrimidine from X. The position of the halogen atom introduced into III and IX was determined by analogy with the previous observations.[11] Further evidence for the orientation of an introduced halogen atom can be provided by the bathochromic shift of the UV absorptions caused by the extra halogen atom, which will be discussed later. Relatively sharp m.ps of the crude products, indicate that there is no competitive halogenation between the benzene ring and pyrimidine nucleus.

Chlorination of monoaminopyrimidines (XII, XIII, and XIV) and 2-amino-4-hydroxy-6-methylpyrimidine (XI) by NCS also gave the 5-chloro derivatives. Brominations of these pyrimidines by NBS were reported previously.[10]

[14] D. Lipkin, F. Howard, D. Nowotny and M. Sano, *J. Biol. Chem.* **238**, 2249 (1963).

2-Morpholino-4,6-dimethyl- or 2-piperidino-4,6-dimethylpyrimidines (V and VI), in which no potentially tautomeric substituent is present, react with NCS or NBS and yield the chloro- or bromo-pyrimidines in good yield. 2-n-Butylamino-4,6-dimethylpyrimidine (VII) is less reactive to NCS than V or VI. Conversion of each of these pyrimidines into chloro-pyrimidines by NCS was examined by vapour-liquid chromatography (VLC) and is shown in Table 1. Although experiments for this comparison were carried out in macro-scale, the yield of the actually isolated chloropyrimidines is compatible with the value predicted from VLC.

TABLE 1. CONVERSION OF PYRIMIDINES V, VI, VII, XV AND XVIII INTO CHLOROPYRIMIDINES BY NCS

Pyrimidine substrate	Conversion (%)
V	100
VI	100
VI	80
XV	5
XVIII	20

The UV spectra of V, VI, and VII showed two bands, one at 240–250 mμ and the other at 300–310 mμ. Both absorptions shifted to higher wavelength in the halogenated compounds, suggesting C-5 as the position of attachment of the halogen atom in keeping with the observation of Boarland and McOmie that the halogen atom at the C-5-position brings about a bathochromic shift and increase of intensity of absorptions of pyrimidine itself.[15]

The IR spectra of these halogenopyrimidines lack absorptions which are found in V (1163 and 819 cm^{-1}) and VI (1170 and 813 cm^{-1}) and assignable to the C-H in-plane and out-of-plane deformation vibrations of a pyrimidine ring.[16] The NMR spectra provide conclusive evidence for the attachment of a halogen atom. This is illustrated by VI and its bromo compound as an example. The spectrum of VI in carbon tetrachloride exhibits methyl protons at τ 7·80, methylene protons adjacent to nitrogen at τ 6·20 as an insufficiently resolved triplet (J = 6 c/s), methylene protons at τ 8·40 as a broad peak and a proton at the C-5-position of a pyrimidine ring at τ 3·93. This latter signal was not present and methyl protons appeared at the downfield (τ 7·60) in the spectrum of the brominated compound of VI. From these spectral observations it is concluded with certainty that the halogen atom is at the C-5-position of a pyrimidine ring.

4-*p*-Chloroanilino-6-methylpyrimidine (IV) gave a monobromo compound, the UV spectrum of which showed a slight hypsochromic shift. In the NMR spectrum of IV in dimethyl sulfoxide the C-5-hydrogen of a pyrimidine ring appears at τ 3·32, which shows a fine structure, thus suggesting the long-range coupling (J = 1·2 c/s) with the C-2-hydrogen of a pyrimidine nucleus. The signal of the C-2-proton is observed at τ 1·39, again showing a fine structure. The benzene ring hydrogens appear as a doublet at τ 2·60 (J = 9·6 c/s) and an another doublet at τ 2·18 (J = 9·0 c/s). Each of these benzene proton signals are further splitted (J = 2·4 c/s). However, the spectrum of the bromo compound exhibits the same benzene ring protons as those of IV, which indicate that there is no extra substituent in the benzene ring, but shows

[15] M. Boarland and J. McOmie, *J. Chem. Soc.* 3716 (1952).
[16] A. Katritzky, *Quart. Revs.* **13**, 353 (1959).

no signals at τ 3·32 and lacks the fine structure of the C-2-proton (τ 1·56). Therefore, it is assumed that bromination has occurred at the C-5-position of a pyrimidine ring, although the UV absorption is incompatible with the general spectral behaviour of 5-halogenopyrimidines (*vide infra*). This anomaly is now under investigation.

These reactions suggest that single primary or secondary amino group is sufficient to enhance the electron availability at the C-5-position of a pyrimidine ring and thus for the chlorination or bromination by NCS or NBS.

Alkoxypyrimidines behave differently from the pyrimidines discussed so far. The reaction of 2-ethoxy-4,6-dimethylpyrimidine (XV) with NBS proceeds more slowly in acetic acid at 100°, much slower in chloroform at reflux temperature, than in the case of other pyrimidines. The reaction course was traced by VLC (Fig. 1). Although the bromo compound was not separated in a perfectly pure state even from the reaction in acetic acid, its formation (mol. wt. 231) is certain from the appearance of

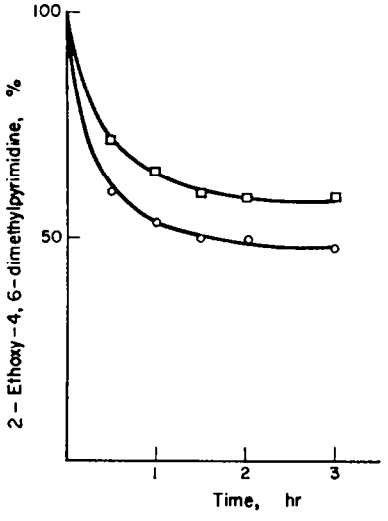


FIG. 1. Reaction of 2-ethoxy-4,6-dimethylpyrimidine with NBS; ○, in acetic acid; □, in chloroform.

abundant ion peaks (*m/e* 230 and *m/e* 232) with equal intensity, which are due to the characteristic bromine isotope peaks ($^{79}Br:^{81}Br = 1:1$), in the mass spectrum of the crude bromo compound of XV. The $(230\text{-}CH_3CHO)^+$ and $(232\text{-}CH_3CHO)^+$ ions were also clearly observed.

2,4-Dimethoxy-6-methylpyrimidine (XVIII) reacts easily with NCS or NBS in chloroform, or more favourably in acetic acid. The reaction was again traced by VLC (Fig. 2). The introduced halogen atom should be at the C-5-position. The UV and NMR spectra support this assumption.

Macro-scale experiments show that NCS reacts with XV more slowly than with XVIII (Table 1). It is apparent that the presence of single alkoxy substituent is not so effective as an amino group for the halogenation of pyrimidines with N-halogeno-succinimide. This is in contrast with the benzene series, where the presence of single alkoxy group is sufficient for the bromination of its *ortho* or *para* position by NBS,[17] and suggests that electron depletion by the ring nitrogen atoms is greater than the

[17] N. Buu-Hoi, *Liebigs Ann.* **556**, 1 (1944).

electron donating effect of an alkoxy group. This unfavourable situation is, however, removed by the presence of an additional alkoxy group as is shown in the present study. It is of interest to note that recently Coton *et al.* recorded successful brominations of di- or tri-alkoxypyrimidines with NBS in acetic acid containing acetic anhydride.[18]

The iodination of aminopyrimidines with NIS was also examined. Although 2-amino-4,6-dimethylpyrimidine (XII) afforded a good yield of the 5-iodo compound, other animopyrimidines, such as I, XIII, and XIV gave iodinated products, confirmed by analysis, but repeated recrystallizations decreased their iodine contents gradually, showing the instability of the carbon–iodine linkage of iodopyrimidines. Recently another example of iodination of XII by 1,3-diiodo-5,5-dimethylhydantoin in moderate yield was reported by Orazi *et al.*[19]

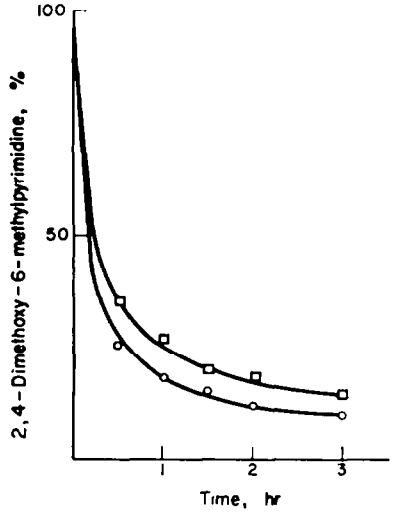


FIG. 2. Reaction of 2,4-dimethoxy-6-methylpyrimidine with NBS; ○, in acetic acid; □, in chloroform.

Bromination of 2-hydroxy-4,6-dimethylpyrimidine (XVI) with sodium hypobromite afforded 2-hydroxy-5-bromo-4,6-dimethylpyrimidine in two modifications, namely colourless and yellow, the formation of which apparently depended on the conditions of acidification.[5] Under all other brominating conditions "perbromides" were formed. Even the treatment of this 5-bromopyrimidine with bromine in chloroform or bromine water led to the formation of "perbromide".

Reaction of XVI, isolated from its hydrochloride and dried over sulfuric acid at room temperature, with NBS in boiling carbon tetrachloride, chloroform, benzene, petroleum ether, or warm acetic acid, yielded a deeply coloured bromine-containing substance, which did not show a definite m.p. Shaking these two compounds in dry chloroform for a short time afforded a clear solution, from which a colourless bromine-containing substance was isolated. This was analysed as $C_6H_7BrN_2O \cdot \frac{1}{2}HBr$ and

[18] M. Caton, M. Grant, D. Pain and R. Slack, *J. Chem. Soc.* 5467 (1965).
[19] O. Orazi, R. Corral and H. Bertorello, *J. Org. Chem.* **30**, 1101 (1965).

exhibited methyl protons (+2·55 ppm from the solvent peak), but showed no C-5-hydrogen in its NMR spectrum in water. With all other solvents no reaction occurred, or a deeply coloured product formed.

However, XVI dried at elevated temperature under reduced pressure gave colourless 2-hydroxy-5-bromo-4,6-dimethylpyrimidine in excellent yield, which probably corresponds to the Stark's colourless modification. The presence of a bromine atom at the C-5-position was shown by the bathochromic shift in the UV absorption and the fact that there was no signal assignable to the C-5-hydrogen in the NMR spectrum determined in deuterochloroform. The methyl protons were observed at τ 7·44.

Similarly, perfectly dry XVI with NCS in dry chloroform yielded a clear solution, which gradually turned orange in the subsequent work-up and no well-defined product was isolated.

Other hydroxypyrimidines selected were 4-hydroxy-6-methylpyrimidine (XVII), uracil, and 6-methyluracil (XIX). Compound XVII afforded 5-chloro, 5-bromo, and 5-iodo compounds by reaction with NCS, NBS, or NIS in chloroform. Similarly, 5-iodouracil and 5-iodo-6-methyluracil were obtained.

The UV spectra of 5-halogenopyrimidines as well as their 5-unsubstituted pyrimidines were examined. The wave-lengths of maximum extinction and the logarithms of the molecular extinction coefficients are recorded in the Table 2. It will be seen that the halogen atom at the C-5-position of a pyrimidine ring generally causes a bathochromic shift of the absorption band irrespective of the kind of substituents at the 2-, 4-, and 6-positions. This is in agreement with the observation of Boarland and McOmie.[15,20] The kind of a halogen atom had little effect on the absorption.

It has been reported[15] that for a single substituent, the bathochromic shift varies according to the position of the substituent in the pyrimidine ring and the 2-substituent forms a series which may be written in the order of increasing bathochromic shift: Me < MeS < C_6H_5 < Cl < MeO < S^- < O^- < NH_2. It is clear from Table 2 that for 4-substituted 2-amino-6-methylpyrimidines, one series may be written: OR < OC_6H_4Cl-*p* < morpholino < Me < Cl < NHC_6H_5, while for 4-substituted 2-amino-5-bromo-6-methylpyrimidines, another series may be possible: OR < OC_6H_4Cl-*p* = morpholino = Me < NHC_6H_5 < Cl. Reversal of the order between an anilino and a chloro substituent in 4-substituted 2-amino-5-bromo-6-methylpyrimidines will be due to a certain amount of steric interaction between the 5-bromine atom and the *ortho* hydrogen atom of a 4-anilino group, which will disturb the bathochromic effect of a bromine atom.

For spectral comparison 2-methylthio-4-ethoxy-6-methylpyramidine and its 5-bromo derivative were prepared.

EXPERIMENTAL

M.ps were determined on the Kofler block but are uncorrected. IR spectra were made as nujol mulls. NMR spectra were determined at 60 Mc. Mass spectrum was made with Hitachi RMU 6D mass spectrometer at 80 eV. VLC was carried out on succinate polyester at 200° in He.

Comparison of reaction rate. An appropriate pyrimidine (0·0005 mole) and NCS (0·0005 mole) were heated in refluxing $CHCl_3$ (2 ml) for 5 min and the resulting solution was subjected to VLC.

5-*Unsubstituted pyrimidines*

2-*Amino*-4-*methoxy*-6-*methylpyrimidine* (I). 2-Amino-4-chloro-6-methylpyrimidine (1·43 g) was heated under reflux in MeONa (Na, 0·23 g and MeOH, 20 ml) for 1 hr. Addition of water precipitated

[20] M. Boarland and J. McOmie, *J. Chem. Soc.* 3722 (1952).

TABLE 2. UV SPECTRA OF 5-UNSUBSTITUTED AND 5-HALOGENO-PYRIMIDINES MEASURED IN ETHANOL

Position of substituents					
2	4	5	6	λ_{max} (mμ)	$\log_{10} \varepsilon_{max}$
Me	H	H	H	249[15]	3·45
Me	H	Br	H	218, 266[20]	3·99, 3·32
Me	Me	H	NH_2	270	3·42
Me	Me	Cl	NH_2	278	3·89
Me	Me	Br	NH_2	279	3·51
NH_2	H	H	H	227, 297[15]	4·22, 3·59
NH_2	H	Cl	H	238, 316	4·32, 3·60
NH_2	H	Br	H	238, 316	4·27, 3·48
NH_2	Me	H	Me	290	3·27
NH_2	Me	Cl	Me	304	3·37
NH_2	Me	Br	Me	304	3·43
NH_2	Me	I	Me	305	3·22
NH_2	Cl	H	Cl	296	3·96
NH_2	Cl	Br	Cl	240, 316	4·23, 3·40
NH_2	Cl	H	Me	295	3·50
NH_2	Cl	Cl	Me	310	3·48
NH_2	Cl	Br	Me	310	3·56
NH_2	OMe	H	Me	276	3·56
NH_2	OMe	Cl	Me	289	3·76
NH_2	OMe	Br	Me	289	3·56
NH_2	OEt	H	Me	276	3·56
NH_2	OEt	Br	Me	288	3·40
NH_2	NHC_6H_5	H	Me	262, 300	3·82, 4·11
NH_2	NHC_6H_5	Br	Me	258, 306	3·92, 4·00
NH_2	NHC_6H_4Cl-*o*	H	Me	258, 298	3·81, 4·34
NH_2	NHC_6H_4Cl-*o*	Cl	Me	258, 308	3·20, 3·98
NH_2	NHC_6H_4Cl-*o*	Br	Me	260, 310	4·06, 4·20
NH_2	NHC_6H_4Cl-*m*	H	Me	259, 299	3·50, 4·22
NH_2	NHC_6H_4Cl-*m*	Br	Me	259, 308	3·85, 4·00
NH_2	NHC_6H_4Cl-*p*	H	Me	265, 302	3·75, 4·31
NH_2	NHC_6H_4Cl-*p*	Br	Me	262, 308	3·91, 4·20
H	NHC_6H_4Cl-*p*	H	Me	292	4·30
H	NHC_6H_4Cl-*p*	Br	Me	288	4·35
NH_2		H	Me	288	3·78
NH_2		Br	Me	304	4·13

TABLE 2 (*contd*)

Position of substituents					
2	4	5	6	λ_{max}(mμ)	$\log_{10} \varepsilon_{max}$
NH_2	OC_6H_4Cl-*p*	H	Me	280	3·81
NH_2	OC_6H_4Cl-*p*	Br	Me	304	3·70
H	OH	H	Me	269	3·44
H	OH	Cl	Me	232, 279	3·45, 3·54
H	OH	Br	Me	235, 282	3·46, 3·53
H	OH	I	Me	238, 290	2·75, 2·96
H	NH_2	H	Me	269	3·62
H	NH_2	Br	Me	240, 279	4·04, 3·62
OH	Me	H	Me	296*	3·02
OH	Me	Br	Me	312*	3·52
NHBu-n	Me	H	Me	239, 312	3·72, 3·05
NHBu-n	Me	Cl	Me	246, 317	4·36, 3·42
	Me	H	Me	247, 300	4·15, 3·04
	Me	Cl	Me	252, 313	4·23, 3·11
	Me	Br	Me	255, 314	4·03, 3·08
	Me	H	Me	250, 308	3·83, 2·84
	Me	Cl	Me	256, 320	4·13, 3·12
	Me	Br	Me	258, 319	4·33, 3·16
OMe	OMe	H	Me	258	3·71
OMe	OMe	Cl	Me	270	3·89
OMe	OMe	Br	Me	270	4·06
SMe	OEt	H	Me	258	3·94
SMe	OEt	Br	Me	261	3·87
SMe	OH	H	Me	232, 284	3·63, 3·47
SMe	OH	Br	Me	245, 299	3·39, 3·51
SEt	OH	H	H	230, 281	3·88, 3·82
SEt	OH	Br	H	245, 302	3·46, 3·68

* Measured in water.

a solid (1·13 g, 81%), which was recrystallized from benzene as colourless plates, m.p. 152–154°. (Found: C, 51·42; H, 6·48. $C_6H_9N_3O$ requires: C, 51·78; H, 6·52%.)

2-Amino-4-ethoxy-6-methylpyrimidine (II). 2-Amino-4-chloro-6-methylpyrimidine (1·43 g) was heated under reflux in EtONa (Na, 0·23 g and EtOH, 20 ml) for 40 min. Addition of water precipitated a solid (1·19 g, 78%), which was recrystallized from water as colourless needles, m.p. 36–38°. (Found: C, 49·14; H, 7·73. $C_7H_{11}N_3O.H_2O$ requires: C, 49·11; H, 7·65%.)

2-Amino-4-p-chlorophenoxy-6-methylpyrimidine (III). 2-Amino-4-chloro-6-methylpyrimidine (1·43 g), KOH (0·6 g), and *p*-chlorophenol (6·5 g) were heated for 2 hr on the steam bath. Addition of 10% KOHaq precipitated a solid (2·00 g, 85%), which was recrystallized from AcOEt as colourless plates, m.p. 220–221°. (Found: C, 56·04; H, 4·20. $C_{11}H_{10}ClN_3O$ requires: C, 56·06; H, 4·28%.)

4-p-Chloroanilino-6-methylpyrimidine (IV). 4-Chloro-6-methylpyrimidine (1·88 g) and *p*-chloroaniline (1·88 g) were heated under reflux in water (20 ml) containing conc. HCl (0·5 ml) for 1 hr.[21] Addition of water and basification with conc. NH_4OH deposited crystals (3·17 g, 99%), which were recrystallized from benzene as light-greenish prisms, m.p. 188–189°. (Found: C, 60·40; H, 4·60. $C_{11}H_{10}ClN_3$ requires: C, 60·14; H, 4·59%.)

2-Morpholino-4,6-dimethylpyrimidine (V). 2-Chloro-4,6-dimethylpyrimidine (3·10 g) and morpholine (2·00 g) were heated under reflux in water (15 ml) for 1·5 hr. Basification of this mixture with 10% NaOHaq yielded a precipitate (4·16 g, 100%), m.p. 43–46° which on distillation at 96°/1·5 mm afforded the pure compound, m.p. 56–57°. (Found: C, 62·09; H, 7·77; N, 22·00. $C_{10}H_{15}N_3O$ requires: C, 62·15; H, 7·82; N, 21·75%.)

2-Piperidino-4,6-dimethylpyrimidine (VI). 2-Chloro-4,6-dimethylpyrimidine (3·30 g) and piperidine (5·40 g) were heated at 100° for 2 hr.[22] The reaction mixture was poured into excess of dil. HCl and the solution neutralized to pH 7 with dil. NH_4OH. The solid product (3·26 g, 74%) was recrystallized from aqueous MeOH as colourless needles, m.p. 62·5–63°. (Found: C, 69·07; H, 8·67. $C_{11}H_{17}N_3$ requires: C, 69·07; H, 8·96%.)

2-Methylthio-4-ethoxy-6-methylpyrimidine. 2-Methylthio-4-chloro-6-methylpyrimidine (7·10 g) was heated under reflux in EtONa (Na, 1·0 g and EtOH, 50 ml) for 1 hr. Removal of solvent *in vacuo* and addition of water yielded an oil, which was extracted with ether, dried (Na_2SO_4), and distilled at 82–83°/2 mm to give a pure compound (4·93 g, 64%), m.p. 33–35°. (Found: C, 52·05; H, 6·46. $C_8H_{12}N_2OS$ requires: C, 52·14; H, 6·56%.) Polonovski and Schmitt recorded m.p. 41° for this compound.[23]

2-Ethoxy-4,6-dimethylpyrimidine (XV). This was prepared according to Angerstein,[24] but distilled at 62–63°/3 mm, n_D^{23} 1·4909.

5-Halogenopyrimidines by N-halogenosuccinimide

2-Amino-4-methoxy-5-chloro-6-methylpyrimidine. Compound I (0·56 g) and NCS (0·53 g) were heated under reflux in $CHCl_3$ (5 ml) for 25 min. The solvent was evaporated and the residual oil treated with warm water (7 ml) for a few min, solidified on cooling (0·52 g, 75%). Recrystallization from water afforded the compound as colourless needles, m.p. 138–141° (in a sealed tube). (Found: C, 41·10; H, 4·35. $C_6H_8ClN_3O$ requires: C, 41·51; H, 4·64%.)

2-Amino-4-methoxy-5-bromo-6-methylpyrimidine. Compound I (0·56 g) and NBS (0·71 g) were refluxed in $CHCl_3$ (10 ml) for 30 min. The solvent was evaporated, the residue treated with water (8 ml) on the steam bath for a few min, the water removed by decantation. The residue (0·80 g, 92%) crystallized from water as colourless rods, m.p. 153–155° (in a sealed tube). (Found: C, 33·04; H, 3·83. $C_6H_8BrN_3O$ requires: C, 33·05; H, 3·70%.)

2-Amino-4-ethoxy-5-bromo-6-methylpyrimidine. Compound II (1·32 g) and NBS (1·53 g) were heated under reflux in $CHCl_3$ (20 ml) for 40 min. The solvent was removed and the residue heated with water (20 ml) on the steam bath for 5 min. After slight cooling the solidified material (2·00 g, 100%) was recrystallized from aqueous EtOH as colourless needles, m.p. 108–109°. (Found: C, 35·86; H, 4·22. $C_7H_{10}BrN_3O$ requires: C, 36·22; H, 4·34%.)

2-Amino-4-p-chlorophenoxy-5-bromo-6-methylpyrimidine. Compound III (0·75 g) and NBS (0·57 g)

[21] F. Basford, F. Curd, E. Hoggart and F. Rose, *J. Chem. Soc.* 1354 (1947).
[22] D. Brown and J. Lyall, *Australian J. Chem.* **17**, 794 (1964).
[23] M. Polonovski and H. Schmitt, *Compt. rend.* **232**, 2108 (1951).
[24] S. Angerstein, *Ber. Dtsch. Chem. Ges.* **64**, 797 (1931).

were heated under reflux in $CHCl_3$ (8 ml) for 40 min. The solvent was evaporated and the residue heated in hot water (10 ml) for 5 min. The insoluble material (1·00 g, 100%) recrystallized from aqueous MeOH as colourless needles, m.p. 176–178°. Further two recrystallizations from aqueous MeOH raised its m.p. to 186–187°. (Found: C, 41·96; H, 2·96. $C_{11}H_9BrClN_3O$ requires: C, 42·00; H, 2·88%.)

2-Amino-4-morpholino-5-bromo-6-methylpyrimidine. Compound VIII (1·60 g) and NBS (1·47 g) were heated under reflux in $CHCl_3$ (20 ml) for 45 min. The solvent was removed and the residual oil heated with water (15 ml) on the steam bath for a few min. The solidified material (1·90 g, 85%) was crystallized from AcOEt as colourless prisms, m.p. 178–180°. (Found: C, 39·30; H, 4·70. $C_9H_{13}BrN_4O$ requires: C, 39·57; H, 4·80%.)

2-Amino-4-p-chloroanilino-5-chloro-6-methylpyrimidine. Compound IX (0·50 g) and NCS (0·29 g) were heated in refluxing $CHCl_3$ (7 ml) for 20 min and treated as before to yield crystals (0·57 g, 100%), which were crystallized from EtOH as colourless needles, m.p. 192–193°. (Found: C, 48·74; H, 3·73. $C_{11}H_{10}Cl_2N_4$ requires: C, 49·08; H, 3·75%.)

2-Amino-4,5-dichloro-6-methylpyrimidine. Compound XIII (1·00 g) and NCS (0·92 g) were heated in refluxing $CHCl_3$ (20 ml) for 30 min and treated as before to give the product (1·22 g, 100%). Crystallization from EtOH gave colourless rods, m.p. 211–212° (in a sealed tube). (Found: C, 34·09; H, 2·87. $C_5H_5Cl_2N_3$ requires: C, 33·73; H, 2·83%.)

2-Amino-5-chloro-4,6-dimethylpyrimidine. Compound XII (1·23 g) and NCS (1·34 g) were heated under reflux in $CHCl_3$ (20 ml) for 30 min. The solvent was removed and the residue treated as before to yield the compound (1·28 g, 81%), which crystallized from acetone as colourless plates, m.p. 192–193° (in a sealed tube). (Found: C, 46·24; H, 5·16. $C_6H_8ClN_3$ requires: C, 45·72; H, 5·12%.)

2,4-Dimethyl-5-chloro-6-aminopyrimidine. Compound XIV (1·23 g) and NCS (1·34 g) were heated under reflux in $CHCl_3$ (20 ml) for 25 min and treated as before to give the compound (1·29 g, 82%). This was recrystallized from water as colourless needles, m.p. 166–168° (in a sealed tube). (Found: C, 34·24; H, 6·51; Cl, 17·24. $C_6H_8ClN_3 \cdot 3H_2O$ requires: C, 34·04; H, 6·67; Cl, 16·75%.)

2-Amino-4-hydroxy-5-chloro-6-methylpyrimidine. Compound XI (1·25 g) and NCS (1·34 g) were heated under reflux in $CHCl_3$ (20 ml) for 1 hr. The solvent was removed and the residue heated in water (20 ml) on the steam bath for a few min. The insoluble material (0·92 g, 58%) was recrystallized from water as light-yellow rods. They began to char at ca. 260° but did not melt. (Found: C, 38·10; H, 3·92. $C_5H_6ClN_3O$ requires: C, 37·63; H, 3·79%.)

2-n-Butylamino-5-chloro-4,6-dimethylpyrimidine. Compound VII (1·20 g) and NCS (0·89 g) were heated under reflux in $CHCl_3$ (10 ml) for 10 min. The solvent was evaporated and the residual oil heated in water (10 ml) for a few min. The solidified material (1·12 g, 77%) was distilled at 73–75°/0·3 mm to give the compound, m.p. 40–42°. (Found: C, 56·20; H, 7·50. $C_{10}H_{16}ClN_3$ requires: C, 56·19; H, 7·55%.) Compound VII (0·90 g) and NCS (0·67 g) were treated as before and the residual oil extracted with ether, dried (Na_2SO_4), and converted into picrate with picric acid (1·10 g). The picrate (1·65 g, 74%) was recrystallized from aqueous EtOH as yellow needles, m.p. 99–100°. (Found: C, 43·53; H, 4·46. $C_{16}H_{19}ClN_6O_7$ requires: C, 43·39; H, 4·32%.)

2-Morpholino-5-chloro-4,6-dimethylpyrimidine. Compound V (1·32 g) and NCS (0·93 g) were heated under reflux in $CHCl_3$ (15 ml) for 10 min. The solvent was removed and the residue heated in hot water (10 ml) for a few min. The solidified material (1·41 g, 91%) was recrystallized from MeOH as colourless needles, m.p. 86–88·5°. (Found: C, 53·03; H, 6·34. $C_{10}H_{14}ClN_3O$ requires: C, 52·75; H, 6·20%.)

2-Morpholino-5-bromo-4,6-dimethylpyrimidine. Compound V (0·95 g) and NBS (0·89 g) were left in $CHCl_3$ (10 ml) for a few min at room temp with occasional shaking. A clear solution formed with slight exothermal reaction. After refluxing this mixture for 10 min, $CHCl_3$ was removed and the residue treated as before to yield solid (1·36 g, 100%), which was recrystallized from EtOH as colourless rods, m.p. 109–111°. (Found: C, 44·36; H, 5·31. $C_{10}H_{14}BrN_3O$ requires: C, 44·13; H, 5·19%.)

2-Piperidino-5-chloro-4,6-dimethylpyrimidine. Compound VI (0·42 g) and NCS (0·30 g) were heated under reflux in $CHCl_3$ (10 ml) for 5 min. Solvent was evaporated, the residual oil treated with water (10 ml) for a few min on the steam bath. Solidified material (0·45 g, 94%) was recrystallized from aqueous EtOH as elongated colourless needles, m.p. 57–58°. (Found: C, 58·81; H, 7·39. $C_{11}H_{16}ClN_3$ requires: C, 58·53; H, 7·15%.)

2-Piperidino-5-bromo-4,6-dimethylpyrimidine. Compound VI (0·96 g) and NBS (0·89 g) were shaken in $CHCl_3$ (10 ml) for a few min at room temp. A clear solution formed with slight exothermic reaction. After refluxing the mixture for 10 min, $CHCl_3$ was evaporated and the residue treated as before. The oil was solidified on cooling (1·23 g, 91%) and recrystallized from aqueous EtOH as colourless rods, m.p. 52–53°. (Found: C, 49·00; H, 5·92. $C_{11}H_{16}BrN_3$ requires: C, 48·90; H, 5·97%.)

4-p-Chloroanilino-5-bromo-6-methylpyrimidine. Compound IV (0·44 g) and NBS (0·36 g) were heated under reflux in $CHCl_3$ (5 ml) for 35 min. The solvent was evaporated and the residual oil heated in water (10 ml) on the steam bath for a few min. The water was removed by decantation and the oil when cooled to −20° solidified (0·52 g, 86%) and was recrystallized from aqueous MeOH as colourless needles, m.p. 96–97°. (Found: C, 42·62; H, 3·22; N, 13·16. $C_{11}H_9BrClN_3 \cdot \frac{1}{2}H_2O$ requires: C, 42·95; H, 3·28; N, 13·32%.)

4-Amino-5-chloro-6-methylpyrimidine. Compound X (0·22 g) and NCS (0·27 g) were refluxed in $CHCl_3$ (5 ml) for 20 min. The solvent was removed and the residue treated with water (10 ml) on the steam bath for 5 min. The insoluble material (0·14 g, 50%) was recrystallized from water as colourless rods, m.p. 196–197° (in a sealed tube). Gabriel and Colman recorded m.p. 197–198° for this compound.[35]

2-Amino-5-iodo-4,6-dimethylpyrimidine. Compound XII (1·23 g) and NIS (2·11 g) were refluxed in $CHCl_3$ (20 ml) for 45 min. The solvent was evaporated and the residue heated in water (20 ml) for 10 min, to which 0·1N $Na_2S_2O_3$ (8 ml) was added. After some time the insoluble material was filtered off (1·88 g, 72%) and recrystallized from acetone as slightly yellowish rectangular plates, m.p. 191–192°. (Found: C, 28·99; H, 3·12. $C_6H_8IN_3$ requires: C, 28·93; H, 3·24%.) Orazi *et al.* recorded m.p. 182–183° for this compound.[19]

Attempted iodination of 2,4-dimethyl-6-aminopyrimidine. Compound XIV (1·23 g) and NIS (2·11 g) were refluxed in $CHCl_3$ (20 ml) for 40 min, during which time the isolation of free I_2 was noticed. The insoluble material (2·07 g, 83%) was filtered off and washed with $CHCl_3$, m.p. 148–151° (Found: I, 50·35%). Recrystallization from benzene gave light-yellow needles, m.p. 130–130·5°. (Found: I, 45·18%) and the mother liquor turned red. Further several recrystallization lowered the I_2 content gradually.

Attempted bromination of 2-ethoxy-4,6-dimethylpyrimidine. Compound XV (1·52 g) and NBS (1·78 g) were heated in glacial AcOH (20 ml) at 100° for 3 hr. The reaction mixture was poured into water (100 ml) and neutralized with 20% NaOHaq. The oil was extracted with ether, dried (Na_2SO_4), and distilled at 81–83°/2 mm to give the crude bromo compound of XV (0·5 g).

2,4-Dimethoxy-5-chloro-6-methylpyrimidine. Compound XVIII (1·54 g) and NCS (1·34 g) were heated in AcOH (20 ml) at 100° for 1·5 hr and the reaction mixture was poured into water (100 ml). Crystals (1·09 g, 58%) were collected and recrystallized from aqueous MeOH as colourless needles, m.p. 66·5–69°. (Found: C, 44·34; H, 4·92. $C_7H_9ClN_2O_2$ requires: C, 44·57; H, 4·81%.)

2,4-Dimethoxy-5-bromo-6-methylpyrimidine. Compound XVIII (3·08 g) and NBS (3·56 g) were heated in AcOH (30 ml) at 100° for 2 hr and the reaction mixture was poured into water (100 ml). Crystals (3·70 g, 78%) were filtered off and recrystallized from pet. ether (b.p. 30–60°) and then from aqueous acetone as colourless needles, m.p. 75–76°. (Found: C, 35·66; H, 4·01; Br, 34·00. $C_7H_9BrN_2O_2$ requires: C, 35·46; H, 3·83; Br, 33·71%.)

Bromination of 2-hydroxy-4,6-dimethylpyrimidine. (a) Compound XVI (1·24 g) dried over H_2SO_4 at room temp and NBS (1·78 g) were shaken in dry $CHCl_3$ (20 ml) for 15 min, during which time all the solid dissolved. The solvent was evaporated at room temp and the residue heated in dry AcOEt (20 ml) for 15 min. The insoluble material (1·40 g), which turned black at ca. 130° but showed no definite m.p., was recrystallized 3 times from absolute EtOH to yield colourless needles. This compound turned at ca. 160° to a black material but did not melt even at 300°. (Found: C, 29·90; H, 2·93; N, 11·65; Br, 49·63. $C_6H_7BrN_2O \cdot \frac{1}{2}HBr$ requires: C, 29·59; H, 3·10; N, 11·51; Br, 49·23%.) This compound turned into a red material during the storage over H_2SO_4. The recrystallization mother liquor evolved an irritating odour.

(b) Compound XVI (1·00 g) dried over P_2O_5 at 140° at the press of 25 mm for 12 hr and NBS (1·44 g) were added in dry $CHCl_3$ (20 ml) and shaken occasionally for 20 min at room temp, during which time all the solid material dissolved. The solvent was evaporated at room temp and the

[35] S. Gabriel and J. Colman, *Ber. Dtsch. Chem. Ges.* **34**, 1238 (1901).

residue heated in dry AcOEt (25 ml) for 15 min. The insoluble material (1·52 g, 93%) was recrystallized from water as colourless plates, m.p. 220–223° (dec). (Found: C, 35·41; H, 3·41; N, 13·70. $C_6H_7BrN_2O$ requires: C, 35·49; H, 3·48; N, 13·80%.) Stark recorded m.p. 228–231° (dec) for this compound.[8]

4-Hydroxy-5-chloro-6-methylpyrimidine. Compound XVII (0·55 g) and NCS (0·67 g) were heated under reflux in $CHCl_3$ (10 ml) for 45 min. The solvent was evaporated and the residue heated in AcOEt (15 ml) for 5 min. The insoluble material (0·50 g, 70%) was recrystallized from EtOH as colourless plates, m.p. 209–211°. (Found: C, 41·61; H, 3·45. $C_6H_5ClN_2O$ requires: C, 41·54; H, 3·49%.)

4-Hydroxy-5-bromo-6-methylpyrimidine. Compound XVII (1·10 g) and NBS (1·78 g) were refluxed in $CHCl_3$ (20 ml) for 40 min. The solvent was removed and the residue treated with hot water (20 ml) for 10 min. The insoluble material (1·25 g, 66%) crystallized from acetone as colourless plates, m.p. 232–233°. (Found: C, 32·20; H, 2·62. $C_6H_5BrN_2O$ requires: C, 31·77; H, 2·67%.)

4-Hydroxy-5-iodo-6-methylpyrimidine. Compound XVII (1·10 g) and NIS (2·11 g) were refluxed in $CHCl_3$ (20 ml) for 30 min and treated as before to give the product (1·70 g, 72%), which recrystallized from water as colourless rods, m.p. 238–239° (dec). (Found: C, 25·62; H, 2·14. $C_6H_5IN_2O$ requires: C, 25·44; H, 2·14%.)

5-Iodo-6-methyluracil. Compound XIX (0·73 g) and NIS (1·23 g) were heated under reflux in $CHCl_3$ (15 ml) for 45 min. The solvent was evaporated and the residue treated in water (15 ml) for a few min on the steam bath. The insoluble material (1·12 g, 88%) was recrystallized from water as colourless plates, m.p. 280–283° (dec). (Found: C, 23·30; H, 1·93; I, 48·80. $C_5H_5IN_2O_2 \cdot \frac{1}{2}H_2O$ requires: C, 23·01; H, 1·93; I, 48·62%.)

5-Iodouracil. Uracil (0·66 g) and NIS (1·13 g) were heated under reflux in $CHCl_3$ (10 ml) for 1 hr and treated as before to give the product (0·67 g, 56%). This was recrystallized from water as colourless needles, m.p. 270–273° (dec). (Found: C, 20·12; H, 1·31; I, 53·40. $C_4H_3IN_2O_2$ requires: C, 20·19; H, 1·27; I, 53·32%.)

5-Halogenopyrimidine by other procedure

2-Methylthio-4-ethoxy-5-bromo-6-methylpyrimidine. 2-Methylthio-4-chloro-5-bromo-6-methylpyrimidine (4·30 g) was heated in EtONa (Na, 0·7 g and EtOH, 25 ml) for 1 hr. Addition of water and removal of solvent left an oil, which was extracted with ether, dried (Na_2SO_4), and distilled at 122–125°/3 mm to yield the compound, 3·34 g, 80%. (Found: C, 36·82; H, 4·36. $C_8H_{11}BrN_2OS$ requires: C, 36·51; H, 4·21%.)