915. *Pyrimidines. Part IV.* Experiments on the Synthesis of Pyrimidine and 4 : 6-Dimethylpyrimidine.*

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Several methods for the preparation of pyrimidine and 4 : 6-dimethylpyrimidine have been investigated. Although most of them are of theoretical interest only, 4 : 6-dimethylpyrimidine can be prepared in good yield by the catalytic reduction of the corresponding 2-chloro-compound.

A new method for the isolation of pyrimidines from aqueous solution is described.

The results of bacteriological tests on a variety of pyrimidines are recorded.

Pyrimidine and its methyl derivatives are generally prepared by reductive dehalogenation of the chloro-compounds derived from readily accessible oxy-derivatives. The final dehalogenation almost invariably lowers the yield, often rendering the method impracticable, and only very recently has this difficulty been overcome (Whittaker, *J.*, 1951, 1565; Lythgoe and Rayner, *J.*, 1951, 2323). We have therefore investigated other methods (both direct and indirect) for the removal of halogen from the pyrimidine ring. Although most of these have not proved of practical value, they appear worth reporting, together with some investigations into the more conventional methods of dehalogenation.

Pyrimidine.—A general method for replacing an active chlorine atom in heterocyclic compounds by hydrogen has been described by Albert and his co-workers (*J.*, 1949, 1148, 1284). Benzenesulphonhydrazide and 2 : 4-dichloropyrimidine condensed smoothly in ethanol; alkaline hydrolysis of the bisbenzenesulphonhydrazino-derivative gave a 66% yield of pyrimidine, isolated as its mercuric chloride complex. The identity of the complex obtained in this and all following experiments was confirmed by means of *X*-ray powder photographs (see Table 1).

Table 1. *X-Ray spacings* (Å) *corresponding to the three most intense lines for mercuric chloride complexes of pyrimidine derivatives, etc.*

Pyrimidine		4 : 6-Dimethylpyrimidine		Trimethylenediamine		Unidentified compound [b]	
d	*I* [a]	*d*	*I*	*d*	*I*	*d*	*I*
7·1	10	8·2	10	8·5	10	7·1	10
6·59	9	5·32	9	4·12	9	6·56	8
4·83	10	3·92	8	2·90	8	4·79	9

[a] Estimated visually, the value 10 being given to the strongest line. [b] Product from the desulphurisation of 2-mercaptopyrimidine.

Although Schofield and Swain (*J.*, 1950, 392) have described the oxidation of 4-cinnolylhydrazines by aqueous copper sulphate to the corresponding cinnolines, only a negligible yield of pyrimidine–mercuric chloride complex was obtained from 2 : 4-dihydrazinopyrimidine.

Raney nickel has frequently been used to remove mercapto- or alkylthio-groups in the pyrimidine series (*e.g.*, Brown *J. Soc. Chem. Ind.*, 1950, **69**, 353). However, the readily available 2 : 4-dithiouracil (Boarland and McOmie, *J.*, 1951, 1218) gave only a low yield of pyrimidine. Cavalieri and Bendich (*J. Amer. Chem. Soc.*, 1950, **72**, 258) mentioned this reaction but gave no details of their yield or method. Desulphurisation of dithiouracil in ethanol gave no pyrimidine; similarly, 2-mercapto-4 : 6-dimethylpyrimidine (see below) and 5-amino-2-ethylthio-4-hydroxypyrimidine (Part V, in the press) were desulphurised in aqueous solution, but were unaffected by Raney nickel in neutral alcohol. The action of Raney nickel on 2-mercaptopyrimidine is described in the Experimental section. An attempt to prepare 2-mercaptopyrimidine directly by the condensation of sodiomalondialdehyde (Gaspar, U.S.P. 2,465,586/1949) and thiourea in the presence of sodium ethoxide was unsuccessful.

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It is of interest that Raney nickel removed not only the alkylthio-group, but also the 5-bromine atom, from 5-bromo-2-methylthiopyrimidine, a low yield of pyrimidine being thus obtained (McOmie and White, forthcoming publication).

Catalytic reduction of 2 : 4-dichloropyrimidine was attempted under a wide variety of conditions, but good reproducible yields of pyrimidine could not be obtained. Recently Whittaker (*loc. cit.*) has successfully dehalogenated chloropyrimidines by using magnesium oxide as the hydrogen chloride acceptor.

In experiments on the catalytic reduction of 2-chloropyrimidine with different catalysts, solvents, and hydrogen chloride acceptors, use of magnesium oxide was found to give 70—80% yields of pyrimidine–mercuric chloride complex with palladium–strontium carbonate, –charcoal, or –barium sulphate. Raney nickel gave negligible yields. Dehalogenation of 2-chloropyrimidine with palladium on polyvinyl alcohol (Rampino and Nord, *J. Amer. Chem. Soc.*, 1941, **63**, 2745) proceeded smoothly, although the yield of pyrimidine was only 58%. In all these experiments, it was necessary to stop the reduction when 1 mol. of hydrogen had been absorbed since the rate of hydrogen uptake did not then decrease. This is probably the simplest method of preparing small quantities of pyrimidine, owing to the ready availability of 2-chloro- from 2-amino-pyrimidine (U.S.P. 2,477,409/1949).

In the present work it was found that the pyrimidine–mercuric chloride complex is soluble in aqueous sodium chloride and dilute hydrochloric acid; consequently, pyrimidine was always isolated by steam-distillation from alkaline solution before precipitation with mercuric chloride.

4 : 6-*Dimethylpyrimidine.*—2-Hydrazino-4 : 6-dimethylpyrimidine was oxidised by copper sulphate, giving a 62% yield of 4 : 6-dimethylpyrimidine–mercuric chloride complex. However, the reaction has to be carried out in aqueous solution and the pyrimidine must be isolated as its complex with mercuric chloride or with 2′-hydroxy-2 : 4 : 7 : 4′-pentamethylflavan (see below) and subsequently regenerated.

The optimum conditions for the desulphurisation of 2-mercapto-4 : 6-dimethylpyrimidine by Raney nickel in aqueous solution (see Experimental) gave *ca.* 70% yields of the mercuric chloride complex. The use of acidic ethanol had the advantage that the pyrimidine

TABLE 2. *Agar-cup diffusion tests on pyrimidines.*

N.A. = nutrient agar; F.B. = fresh blood agar. D = diameter (mm.) of inhibition ring; cup = 8 mm.

Pyrimidine [1]	Concn.[2] (%)	*Staph. aureus*	Other organisms	
[Penicillin]	0·0006	N.A. 31		
2-Mercapto-	0·25	N.A. 25·9 F.B. 19·6	Resistant *Staph. aureus*[3]	N.A. 21·8 F.B. 19·9
			Salmonella dysenteriae, var. Sonne	N.A. 14·5 F.B. 13·6
			Str. viridans	F.B. 25·2
			Mycobact. smegmatis	F. B. 18·4
2-Mercapto-4 : 6-dimethyl-	1·0	N.A. 18·7	Resistant *Staph. aureus*	N.A. 16·8
S-(4 : 6-Dimethyl-2-pyrimidyl)thiuronium chloride	1·0	N.A. 19·2	,, ,,	N.A. 14·4
2 : 4-Dimercapto-	<0·25	N.A. 11·3	,, ,,	N.A. trace
5-Chloro-2-mercapto-	<0·5	N.A. 19·7	,, ,,	N.A. 16·9
4 : 6-Dimercapto-	1·0	N.A. 11·6	,, ,,	N.A. 10·3
S-(4-Mercapto-6-pyrimidyl)thiuronium chloride	<0·25	N.A. 11·5	,, ,,	N.A. trace
2-Hydrazino-4 : 6-dimethyl-	1·0	N.A. 21·7 (hazy)	,, ,,	? (ill-defined)
2 : 4-Dihydrazino-	1·0	N.A. 27·1	,, ,,	26·8
	0·5	N.A. 23·0	,, ,,	22·9
	0·25	N.A. 18·9	,, ,,	17·5

[1] The following showed no zone of inhibition when tested in *ca.* 0·5% solution: 2- and 4-hydroxy-, 4 : 6-dihydroxy-, 4-hydroxy-2-mercapto-, 5-amino-4-hydroxy-, 5-amino-2-ethylthio-4-hydroxy-, 2-amino-, and 2-amino-4 : 6-dimethyl-pyrimidine, 4 : 6-dimethyl-2-pyrimidylthioacetic acid, 4-hydroxypyrimidine-5-carboxylic acid, and 4-hydroxy-2-mercaptopyrimidine-5-carboxylic acid. [2] Solutions were prepared in M/15-phosphate buffer of pH 6·98. If necessary a few drops of alkali were added to make the solution neutral. Some of the compounds did not dissolve completely; these are indicated by the sign <. [3] A strain of Staphylococcus resistant to penicillin, streptomycin, aureomycin, and chloramphenicol.

could be isolated directly from the reaction mixture, and yields of *ca.* 50% of the 4 : 6-dimethylpyrimidine were thus obtained.

2-Chloro-4 : 6-dimethylpyrimidine could be dehalogenated in good yield by catalytic hydrogenation under pressure, and this is a convenient method for preparation of 4 : 6-dimethylpyrimidine in quantity.

Isolation of Pyrimidines from Aqueous Solution.—The suggestion (Baker, Curtis, and Edwards, *J.*, 1951, 83) that the crystalline molecular complexes formed by 2′-hydroxy-2 : 4 : 4 : 7 : 4′-pentamethylflavan with many amines (and certain ethers and ketones) might find application in the isolation and purification of these compounds was followed up. Pyrimidine and 4 : 6-dimethylpyrimidine readily gave complexes of constitution, flavan : H_2O : base = 2 : 2 : 1 and 2 : 1 : 1 respectively. 2-Methylpyrimidine, although not forming an adduct with this flavan, readily gave an anhydrous complex, $C_{20}H_{24}O_2 : C_5H_6N_2 = 2 : 1$, with 2′-hydroxy-2 : 4 : 4 : 6 : 5′-pentamethylflavan. (As with dioxan and morpholine, the bifunctional pyrimidine derivatives form complexes containing two mols. of flavan instead of the usual 1 : 1 adduct.) The pyrimidine derivatives can thus be extracted from dilute aqueous solution in high yield, and may be recovered in a very pure state by distillation of the complex. These flavan complexes possess many advantages over those with mercuric chloride and may prove valuable in the bulk preparation of pure pyrimidines.

Bacteriological results are given in Table 2.

Experimental

M. p.s are uncorrected. Microanalyses are by Mr. W. M. Eno, Bristol, and Drs. Weiler and Strauss, Oxford.

Preparation and Hydrolysis of 2 : 4-Bisbenzenesulphonhydrazinopyrimidine.—2 : 4-Dichloropyrimidine (3·0 g.) and benzenesulphonhydrazide (10·8 g.; Lorenzen, *J. pr. Chem.*, 1898, **58**, 166) in ethanol (20 c.c.), when heated under reflux for 2 hours and then concentrated, gave a colourless product (6·9 g.), m. p. 219° (decomp.), which could not be recrystallised. The impure 2 : 4-bisbenzenesulphonhydrazinopyrimidine (1·0 g.) was heated under reflux with a ten-fold excess of N-sodium hydroxide (50 c.c.) for 1 hour. The initially red solution had then become yellow and evolution of nitrogen had ceased. The solution was distilled, about 35 c.c. of distillate being collected. This was treated with saturated aqueous mercuric chloride and the resulting pyrimidine–mercuric chloride complex (needles) collected (66%).

2 : 4-*Dihydrazinopyrimidine.*—Hydrazine hydrate (8 c.c.; 100%) was slowly added to 2 : 4-dichloropyrimidine (4·0 g.) in ethanol (25 c.c.), a vigorous exothermic reaction occurring. On cooling, the mixture solidified in small needles (1·4 g.). 2 : 4-*Dihydrazinopyrimidine* formed prisms, m. p. 211—212° (decomp.), from water (Found : C, 34·4; H, 5·8; N, 60·0. $C_4H_8N_6$ requires C, 34·3; H, 5·7; N, 60·0%), giving deeply coloured complexes with metal ions (nickel, iron, copper, etc.).

Oxidation. 10% Aqueous copper sulphate (8·0 c.c.) was added dropwise to dihydrazinopyrimidine (0·5 g.) in boiling water (5·0 c.c.), and the dark brown solution was heated for a further 30 minutes. After filtration, the solution was made alkaline with sodium hydroxide and distilled. The distillate gave only a few mg. of pyrimidine–mercuric chloride complex.

Desulphurisation of 2 : 4-Dithiouracil.—2 : 4-Dithiouracil (5·0 g.) was suspended in water (200 c.c.) at 50° and the pH adjusted to *ca.* 7 with sodium carbonate. Raney nickel (23 g.) was added and the mixture heated under reflux for 2 hours. After filtration, the pale yellow solution was distilled, giving an unpleasant smelling, strongly basic distillate which gave the pyrimidine–mercuric chloride complex as needles (17·2%). No trimethylenediamine was isolated (see Table 1).

Desulphurisation of 2-Mercaptopyrimidine.—To 2-mercaptopyrimidine (0·5 g.), dissolved in warm water (50 c.c.) and ethanol (5 c.c.), Raney nickel (2 g.) was added and the mixture heated under reflux for 1½ hours. The colour, which was bright green after addition of the nickel, gradually faded to pale yellow. After filtration, the solution was made alkaline and distilled, yielding a mercuric chloride complex, plates (0·7 g.). An *X*-ray powder photograph showed very slight differences from that of the pyrimidine–mercuric chloride complex (see Table 1). The possibility that a di- or tetra-hydropyrimidine had been formed was not further investigated.

Isolation of a Reineckate from the Catalytic Reduction of 2 : 4-Dichloropyrimidine.—This pyrimidine (2·0 g.) with palladium–strontium carbonate (2·0 g.) and sodium succinate (2·4 g.)

in ethanol (10 c.c.) was hydrogenated at 110 lb./sq. in. for 1¼ hours. No dichloropyrimidine then remained. After filtration the solution was acidified with dilute hydrochloric acid and treated with a saturated aqueous solution of Reinecke's salt. The *reineckate* was precipitated as pink plates (3·1 g.), which crystallised from aqueous acetone as bright pink prisms, m. p. 284—286° (decomp.) (Found: C, 24·5; H, 3·9; N, 27·7; Cr, 15·6. $C_{10}H_{19}N_{10}S_4Cr$ requires C, 24·7; H, 3·9; N, 28·8; Cr, 16·3%). The base, which was not volatile in steam, was not investigated further.

2-Hydrazino-4 : 6-dimethylpyrimidine.—Hydrazine hydrate (3 c.c.; 100%) was slowly added to 2-chloro-4 : 6-dimethylpyrimidine (2·0 g.; Matsukawa and Ohta, *J. Pharm. Soc. Japan*, 1949, **69**, 491) in ethanol (25 c.c.). The felted needles (88%) which formed were collected after 2 hours. Recrystallisation from water gave *2-hydrazino-4 : 6-dimethylpyrimidine* as needles, m. p. 165° (Found: C, 52·0; H, 7·4; N, 40·2. $C_6H_{10}N_4$ requires C, 52·4; H, 7·25; N, 40·4%).

Oxidation. 10% Aqueous copper sulphate (12·5 c.c.) was added dropwise to a boiling solution of 2-hydrazino-4 : 6-dimethylpyrimidine (0·5 g.) in water (10 c.c.). Treatment as in the previous case gave 4 : 6-dimethylpyrimidine–mercuric chloride complex (62%).

Optimum Conditions for the Desulphurisation of 2-Mercapto-4 : 6-dimethylpyrimidine.—A solution of 2-mercapto-4 : 6-dimethylpyrimidine hydrochloride (5·0 g.) in ethanol (100 c.c.) and concentrated hydrochloric acid (2·5 c.c.) was heated under reflux with Raney nickel (15 g.) for 2 hours, then filtered and concentrated to *ca.* 10 c.c. The residue was treated with solid sodium hydroxide and extracted with ether. The ether was removed from the dried extract, leaving a yellow oil, b. p. 156—157°/746 mm. (54%). Angerstein (*Ber.*, 1901, **34**, 3956) reports b. p. 159·5°/754 mm.

Desulphurisation in neutral methanol was unsuccessful owing to the formation of an orange nickel complex from 1 atom of nickel and 2 molecules of the 2-mercapto-compound with the loss of 2 hydrogen atoms [Found: C, 42·4; H, 4·1; N, 17·0; Ni, 17·7 (dimethylglyoxime), 17·3 (residue from C and H determination). Calc. for $C_{12}H_{14}N_4S_2Ni$: C, 42·8; H, 4·2; N, 16·65; Ni, 17·5%]. The compound was soluble in methanolic ammonia, giving a greenish-blue solution, and insoluble in sodium hydroxide. This complex has been briefly described by Jensen and Rancke-Madsen (*Z. anorg. Chem.*, 1934, **219**, 243).

Catalytic Reduction of 2-Chloro-4 : 6-dimethylpyrimidine.—Palladium–charcoal (15 g.; 2·5%) and sodium acetate (15 g.) were added to a solution of 2-chloro-4 : 6-dimethylpyrimidine (15 g.) in ethanol (150 c.c.). The mixture was hydrogenated at 100 lb./sq. in. for 7 hours. After filtration, the solution was made alkaline with sodium hydroxide and the ethanol removed by distillation. The residue was extracted with ether (4 × 100 c.c.) and the extract dried. Distillation gave 4 : 6-dimethylpyrimidine (58%) as a colourless oil, m. p. *ca.* 0°.

Cupric Chloride–4 : 6-Dimethylpyrimidine Complex.—A solution of anhydrous cupric chloride (0·7 g.) in ethanol (5 c.c.) was added to pure 4 : 6-dimethylpyrimidine (1·0 g.). A mauve precipitate was immediately formed (1·1 g.). Recrystallisation from ethanol gave the *complex* as violet needles [Found: C, 41·0; H, 4·7; N, 15·9; Cl, 20·0. $(C_6H_8N_2)_2CuCl_2$ requires C, 41·15; H, 4·6; N, 16·0; Cl, 20·3%]. Attempts to form insoluble complexes from the dimethylpyrimidine and aqueous flavianic acid, picric acid, oxalic acid, and 2 : 4 : 7-trinitrofluorenone were unsuccessful.

Preparation of Pyrimidine–Flavan Complexes (with Dr. R. F. Curtis).—*With 2′-hydroxy-2 : 4 : 4 : 7 : 4′-pentamethylflavan.* (*a*) A dilute (*ca.* 10%) aqueous solution of pyrimidine was shaken with a solution of the flavan in light petroleum (b. p. 40—60°) for 1 hour and set aside at 0° for 12 hours. The crystalline complex was collected and recrystallised from light petroleum (b. p. 40—60°) and a drop each of ethanol and water as thick, almost rectangular prisms, m. p. 80—82° (decomp.; sealed tube) [Found: C, 74·9; H, 7·7; N, 3·4. $(C_{20}H_{24}O_2)_2,2H_2O,C_4H_4N_2$ requires C, 74·6; H, 7·9; N, 3·95%]. No complex was obtained in the absence of water.

(*b*) The flavan (1·0 g.) in light petroleum (b. p. 60—80°) (10 c.c.) was treated with impure 4 : 6-dimethylpyrimidine (0·5 c.c.) and seeded after filtration. Tiny colourless rhombs separated immediately (1·12 g.). One recrystallisation gave the pure *complex*, m. p. 105—107° (decomp.) [Found: C, 77·0; H, 7·7; N, 4·0. $(C_{20}H_{24}O_2)_2,H_2O,C_6H_8N_2$ requires C, 76·9; H, 8·1; N, 3·9%].

2-Methylpyrimidine with 2′-hydroxy-2 : 4 : 4 : 6 : 5′-pentamethylflavan. A crystalline *complex* separated immediately from light petroleum (b. p. 40—60°). Recrystallisation from the same solvent gave large rhombs, m. p. 94—96° (decomp.) [Found: C, 78·7; H, 7·7; N, 3·7. $(C_{20}H_{24}O_2)_2,C_5H_6N_2$ requires C, 78·7; H, 7·9; N, 4·1%]. The authors are indebted to Dr. E. C. Kornfeld for a generous gift of 2-methylpyrimidine.

(*4 : 6-Dimethyl-2-pyrimidylthio*)*acetic Acid.*—To 2-mercapto-4 : 6-dimethylpyrimidine (1·0 g.)

in aqueous sodium hydroxide (0·6 g. in 3·0 c.c.), chloroacetic acid (0·7 g.) in water (1·0 c.c.) which had been neutralised with sodium carbonate was added dropwise. Next day, acidification with dilute hydrochloric acid gave (4 : 6-*dimethyl*-2-*pyrimidylthio*)*acetic acid* as prismatic needles, m. p. 112—113° (0·7 g. crude) after recrystallisation from water (Found : C, 45·0; H, 5·4; N, 13·3; S, 14·7. $C_8H_{10}N_2O_2S,H_2O$ requires C, 44·5; H, 5·55; N, 13·0; S, 14·8).

(4 : 6-*Dihydroxy*-2-*pyrimidylthio*)*acetic Acid*.—This *compound*, prepared from 4 : 6-dihydroxy-2-mercaptopyrimidine as described above, crystallised from water as needles, m. p. 205° (decomp.) (Found : C, 36·0; H, 3·2; N, 14·2. $C_6H_6N_2O_4S$ requires C, 35·7; H, 3·0; N, 13·85%).

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