68. *New Cytotoxic Agents with Tumour-inhibitory Activity. Part I. Some Aziridinopyrimidine Derivatives.*

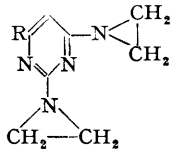
By J. A. Hendry and R. F. Homer.

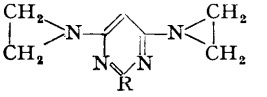
The reaction of ethyleneimine with a number of chloropyrimidines has given the corresponding aziridinopyrimidines. Those products which have in the molecule two ethyleneimine residues show a marked inhibiting effect on the growth of the Walker carcinoma 256 in rats, and cause abnormalities of the radiomimetic type in dividing cells. The nitration of a number of 2-aryl-4 : 6-dihydroxypyrimidines has been investigated, and some new 2-aryl-4 : 6-dichloro- and 2-aryl-4 : 6-dichloro-5-nitropyrimidines are described.

The discovery in these and other laboratories of tumour-inhibitory and cytotoxic activity of the radiomimetic type in a number of cross-linking agents which also have the capacity to polymerise, for example, poly(hydroxymethylamides) and bis(ethylene oxides) (Rose, Hendry, and Walpole, *Nature*, 1950, **165**, 993; *Brit. J. Pharmacol.*, 1951, **6**, 201; Hendry, Homer, Rose, and Walpole, *ibid.*, p. 235; Ross, *J.*, 1950, 2257), has led us to examine a number of ethyleneimine derivatives as further examples of this type of compound. As various aziridinotriazines have been shown to have this type of activity (Rose, Hendry, and Walpole, *loc. cit.*; Burchenal, Stock, Crossley, and Rhoads, *Cancer Res.*, 1950, **10**, 207; Burchenal, Johnston, Stock, Crossley, and Rhoads, *ibid.*, p. 208), work on similar

derivatives of the biologically important pyrimidine nucleus followed, and this paper describes their preparation.*

The reaction between ethyleneimine and chloropyrimidines has been found to proceed readily in the presence of alkali, according to the method worked out by Bestian (*Annalen*, 1950, **566**, 210) for other compounds containing active chlorine atoms, provided that the halogen is sufficiently activated by the remainder of the molecule for reaction to occur under conditions which do not lead to polymerisation of the ethyleneimine or of the product. Thus, for example, 4 : 6-dichloro-5-nitropyrimidines react vigorously with ethyleneimine in the cold, both chlorine atoms being replaced; however, with un-nitrated 4 : 6-dichloropyrimidines only one chlorine atom reacts. Of the three chlorine atoms of 2 : 4 : 6-trichloropyrimidine only two can be replaced by ethyleneimine residues, giving 2 : 6-diaziridino-4-chloropyrimidine (I; R = Cl) and all attempts to replace the third chlorine atom by more drastic treatment have led to polymer formation. However, 2 : 6-diaziridino-4-chloropyrimidine reacts readily with sodium alkoxide, yielding (I; R = OAlk). The use of *N*-lithioethyleneimine as a reagent for relatively unreactive chlorine atoms, in accordance with the method of Gilman, Crounse, Massie, Benkeser, and Spatz (*J. Amer. Chem. Soc.*, 1945, **67**, 2106) has succeeded in a few cases, leading to (II; R = Ph and β-$C_{10}H_7$). It has not been possible to replace the third chlorine atom of trichloropyrimidine by this procedure.

(I) 

 (II)

The reaction of a chloropyrimidine with ethyleneimine is best carried out in aqueous alkali, or in benzene in the presence of triethylamine. The optimum reaction temperature appears to be between 30° and 45°, higher temperatures leading to polymerisation either of the ethyleneimine or of the product. It is essential that the reaction mixture at no time becomes acid as this leads to polymerisation or opening of the aziridine ring according to the conditions; the products are, however, stable to alkali, and in most cases can be recrystallised from moderately low-boiling solvents. The pure crystalline products are stable at room temperature for many months.

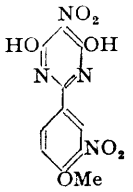
Starting materials were prepared by established general methods. Nitration of the hydroxypyrimidine was rapidly effected with fuming nitric acid in the cold, except in the case of 4 : 6-dihydroxy-2-β-naphthylpyrimidine where fuming acid caused decomposition and nitration was effected with a large excess of ordinary concentrated acid. In the case of 4 : 6-dihydroxy-2-*p*-methoxyphenyl-, 2-*p*-ethoxyphenyl-4 : 6-dihydroxy-, and 4 : 6-dihydroxy-2-*p*-tolyl-pyrimidine two nitro-groups were introduced by this treatment, one at position 5 of the pyrimidine ring and one in the aryl moiety. 4 : 6-Dihydroxy-2-phenyl- and -2-β-naphthyl- and 2-*p*-chlorophenyl-4 : 6-dihydroxy-pyrimidine yielded the 5-mononitro-compounds.

The nitro-group of the mononitro-compounds, and one of the nitro-groups of the dinitro-compounds, is at position 5 of the pyrimidine ring since, whereas the un-nitrated 2-aryl-4 : 6-dihydroxypyrimidines couple in alkaline solution with diazotised *p*-chloroaniline, and also give a yellow colour on treatment with nitrous acid (indicative of a free 5 position, Lythgoe, Todd, and Topham, *J.*, 1944, 315), the nitrated compounds undergo neither of these reactions. Direct proof of the structure of 4 : 6-dihydroxy-2-(4-methoxy-3-nitrophenyl)-5-nitropyrimidine (III) is afforded by oxidation with alkaline permanganate to 4-methoxy-3-nitrobenzoic acid. Similar oxidation of 4 : 6-dihydroxy-5-nitro-2-phenylpyrimidine yielded benzoic acid. The position of the nitro-group in the aryl moiety of 4 : 6-dihydroxy-2-(nitro-*p*-tolyl)-5-nitropyrimidine cannot be found by this method and has not been determined.

The crude hydroxynitropyrimidines which were too insoluble to crystallise in bulk,

* Patents pending.

though analytical samples were recrystallised satisfactorily from aqueous dimethylformamide, were converted smoothly into the corresponding, readily purified 2-aryl-4 : 6-dichloro-5-nitropyrimidines on treatment under reflux with phosphoryl chloride in the presence of dimethylaniline. Direct nitration of 4 : 6-dichloro-2-*p*-ethoxyphenylpyrimidine was effected in low yield by treatment with fuming nitric acid, one nitro-group only being introduced, presumably in the ethoxyphenyl residue, to give 4 : 6-dichloro-2-(4-ethoxy-3-nitrophenyl)pyrimidine (IV).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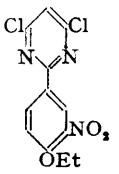
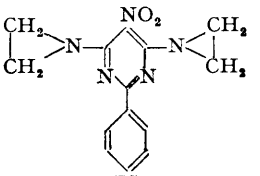

(IV)


(V)

4 : 6-Diaziridino-5-nitro-2-phenylpyrimidine (V) was reduced catalytically over Raney nickel at atmospheric temperature and pressure, without scission of the imine ring, to 5-amino-4 : 6-diaziridino-2-phenylpyrimidine. A similar reduction attempted with 2 : 4-diaziridino-5-nitropyrimidine gave only intractable or polymeric material.

Of the compounds obtained many of those carrying two ethyleneimine residues have been found to inhibit the growth of the Walker carcinoma 256 to a marked extent, and to show cytotoxic properties of the radiomimetic type (cf. Hendry, Homer, Rose, and Walpole, *Brit. J. Pharmacol.*, 1951, **6**, 357).

Experimental

Reaction of 2 : 4 : 6-*Trichloropyrimidine with Ethyleneimine.*—(a) *With* 1 *molecular proportion of ethyleneimine.* A solution of ethyleneimine (4·70 g.) in water (50 c.c.) was added to a suspension of 2 : 4 : 6-trichloropyrimidine (20 g.) in water (125 c.c.) containing sodium carbonate (6·3 g., anhyd.), with stirring at 30—35°. The oily mass which separated solidified after about 20 minutes. The reaction mixture was stirred for a further 0·5 hour, and then filtered, and the solid well washed with water and with a small quantity of ice-cold methanol. Fractional crystallisation from light petroleum (b. p. 60—80°) gave as the least soluble fraction 2-*aziridino*-4 : 6-*dichloropyrimidine* (5·8 g.), m. p. 105° (Found : C, 37·8; H, 2·6; N, 22·3. $C_6H_5N_3Cl_2$ requires C, 37·9; H, 2·6; N, 22·1%), and from the mother-liquors long needles of the isomeric 6-*aziridino*-2 : 4-*dichloropyrimidine* (1·25 g.), m. p. 111° (Found : C, 37·4; H, 2·6; N, 22·0%). The isomers are tentatively assigned these structures by analogy of the m. p. with those of the isomeric aminodichloropyrimidines and dichloromethylaminopyrimidines investigated respectively by Büttner (*Ber.*, 1903, **36**, 2228) and Winkelman (*J. pr. Chem.*, 1927, **115**, 292).

(b) *With* 2 *or more molecular proportions of ethyleneimine.* 2 : 4 : 6-Trichloropyrimidine (20 g.) was added slowly to a solution of ethyleneimine (12·4 g., 2·5 mols.) and triethylamine (29 g., 2·5 mols.) in benzene (100 c.c.) with stirring and cooling to keep the temperature at 25—30°. The reaction mixture was stirred for a further 1·5 hours at 25—30° and then filtered from triethylamine hydrochloride. The filtrate on evaporation under reduced pressure below 35° gave a semi-solid residue of crude product which was repeatedly extracted with boiling light petroleum (b. p. 60—80°). The cooled extracts deposited 2 : 6-*diaziridino*-4-*chloropyrimidine* as colourless plates, m. p. 94—95° (9·5 g., 44%) (Found : C, 49·05; H, 4·75; N, 28·6; Cl, 17·85. $C_8H_9N_4Cl$ requires C, 48·8; H, 4·6; N, 28·5; Cl, 18·1%). Occasionally the syrupy residue from the light petroleum extract polymerised violently after decantation of the solvent, possibly owing to local overheating during the extraction.

Treatment of 2 : 6-*Diaziridino*-4-*chloropyrimidine with Ethyleneimine.*—The pyrimidine (1·96 g.) was heated in benzene (25 c.c.), triethylamine (2·0 g.), and ethyleneimine (0·86 g.) under reflux for 3 hours. The resulting solution was decanted from glassy polymer (1·1 g.) and was evaporated to dryness under reduced pressure. Recrystallisation of the residue gave unchanged material (0·93 g., 47·5%).

2 : 6-*Diaziridino*-4-*methoxypyrimidine.*—2 : 6-Diaziridino-4-chloropyrimidine (8·8 g.) was added to a solution of sodium (1·2 g., 1·1 atoms) in AnalaR methanol (80 c.c.). An immediate cloudiness developed and after 1 hour at 50° the reaction was complete. The reaction mixture

was filtered from sodium chloride and the filtrate evaporated below 40° to a solid residue which on crystallisation from light petroleum (b. p. 60—80°) gave 2 : 6-*diaziridino*-4-*methoxypyrimidine* (3·3 g.) as colourless prisms, m. p. 86°, b. p. 110—120°/0·2 mm. (Found : C, 56·5; H, 6·5; N, 29·3. $C_9H_{12}ON_4$ requires C, 56·3; H, 6·3; N, 29·2%). Similarly prepared were 2 : 6-*diaziridino*-4-*ethoxy*-, b. p. 107°/0·1 mm. (Found : C, 57·8; H, 7·3; N, 26·6. $C_{10}H_{14}ON_4$ requires C, 58·3; H, 6·8; N, 27·2%), and -4-iso*propoxy-pyrimidine*, b. p. 114°/0·05 mm. (Found : N, 26·0. $C_{11}H_{16}ON_4$ requires N, 25·5%).

2 : 4 : 6-*Trichloro*-5-*phenylpyrimidine*.—5-Phenylbarbituric acid (D.R.-P. 247,952; *Frdl.*, **11**, 926) (35 g.) was heated under reflux with phosphoryl chloride (100 c.c.) and dimethylaniline (35 c.c.) for 1 hour, cooled, and poured on ice. The white solid which separated was filtered off and dried in a vacuum over phosphoric oxide. Crystallisation from light petroleum (b. p. 60—80°) gave white needles (23.8 g.) of 2 : 4 : 6-*trichloro*-5-*phenylpyrimidine*, m. p. 160° (Found : C, 46·2; H, 1·75; N, 11·0; Cl, 41·1. $C_{10}H_4N_2Cl_3$ requires C, 46·4; H, 1·5; N, 10·8; Cl, 41·2%).

2 : 6-*Diaziridino*-4-*chloro*-5-*phenylpyrimidine*.—To a solution of ethyleneimine (10 g.) and triethylamine (25 g.) in benzene (200 c.c.) was added 2 : 4 : 6-trichloro-5-phenylpyrimidine (14·6 g.) with stirring at 30—40°. Stirring was continued at 35—40° for 1 hour, the reaction mixture was filtered, and the filtrate evaporated below 40° to a sticky solid. Extraction of this with light petroleum (b. p. 60—80°) yielded, after cooling, a white solid which, crystallised from the same solvent, gave the *diaziridino*-compound (4·0 g.) as needles, m. p. 116—118° (Found : N, 20·2; Cl, 12·8. $C_{14}H_{15}N_4Cl$ requires N, 20·55; Cl, 13·0%).

2-*Aryl*-4 : 6-*dihydroxypyrimidines*.—These compounds were prepared by condensation of ethyl malonate with the appropriate amidine. The following exemplifies the method. Benzamidine hydrochloride (65·2 g.) and ethyl malonate (67 g., 1·1 mols.) were added to a solution of sodium (25·7 g., 3 atoms) in dry ethanol (400 c.c.). After 3 hours' stirring under reflux the solvent was distilled off, the residue taken up in hot water, and the resulting solution acidified with hydrochloric acid. The precipitated 4 : 6-dihydroxy-2-phenylpyrimidine was filtered off, dried at 100°, and recrystallised from aqueous dimethylformamide. It had m. p. 326° (decomp.) (66 g.).

Similarly prepared were : 4 : 6-*dihydroxy*-2-β-*naphthyl*- (98%), m. p. 316—318° (decomp.) (Found : N, 11·2. $C_{14}H_{10}O_2N_2$ requires N, 11·7%), -2-p-*ethoxyphenyl*- (86%), m. p. 289—291° (decomp.) (Found : N, 11·6. $C_{12}H_{12}O_3N_2$ requires N, 12·1%), and -2-p-*tolyl-pyrimidine* (91%), m. p. 310° (decomp.) (Found : N, 13·8. $C_{11}H_{10}O_2N_2$ requires N, 13·85%), all crystallised from aqueous dimethylformamide.

Nitrations.—4 : 6-*Dihydroxy*-5-*nitro*-2-*phenylpyrimidine* [With R. HULL]. 4 : 6-Dihydroxy-2-phenylpyrimidine (34 g.) was added to nitric acid (170 c.c.; *d* 1·5) with cooling and stirring at 10—20°. After 15 minutes' stirring at 20° the mixture was poured on ice and the 4 : 6-*dihydroxy*-5-*nitro*-2-*phenylpyrimidine* (29 g., 68%) filtered off, washed with water, and dried (Found : C, 51·3; H, 3·2; N, 18·3. $C_{10}H_7O_4N_3$ requires C, 51·5; H, 3·0; N, 18·0%). 2-p-Chlorophenyl-4 : 6-dihydroxypyrimidine similarly yielded 2-p-*chlorophenyl*-4 : 6-*dihydroxy*-5-*nitro-pyrimidine* (49%) as a pale yellow powder (from aqueous dimethylformamide), m. p. 300° (decomp.) (Found : C, 44·5; H, 1·7; Cl, 12·6. $C_{10}H_6O_4N_3Cl$ requires C, 44·9; H, 2·2; Cl, 13·2%). Similar treatment of 4 : 6-dihydroxy-2-*p*-methoxyphenylpyrimidine gave 4 : 6-*dihydroxy*-2-(4-*methoxy*-3-*nitrophenyl*)-5-*nitropyrimidine* (42%), as an orange-yellow powder, m. p. 246—248° (decomp.) (Found : N, 18·3. $C_{11}H_8O_7N_4$ requires N, 18·2%). From 4 : 6-dihydroxy-2-*p*-ethoxyphenylpyrimidine was likewise obtained 2-(4-*ethoxy*-3-*nitrophenyl*)-4 : 6-*dihydroxy*-5-*nitropyrimidine* (42%), m. p. 268—270° (decomp.) (from aqueous dimethylformamide) (Found : C, 45·3; H, 3·5; N, 17·3. $C_{12}H_{10}O_7N_4$ requires C, 44·8; H, 3·1; N, 17·4%).

4 : 6-Dihydroxy-2-β-naphthylpyrimidine (28 g.) was added with stirring to nitric acid (560 c.c.; *d* 1·4) at 20°. Stirring was maintained for 20 minutes, the temperature being allowed to rise to 30—35°. The suspension was then poured into ice-water (3 l.) and filtered. Crystallisation of the crude solid from aqueous dimethylformamide gave 4 : 6-*dihydroxy*-2-β-*naphthyl*-5-*nitropyrimidine* (16·8 g.) as a yellow powder, m. p. 328° (decomp.) (Found : C, 59·7; H. 3·3; N, 15·2. $C_{14}H_9O_4N_3$ requires C, 59·4; H, 3·2; N, 14·9%).

Nitration with nitric acid (*d* 1·5) in the usual manner gave 4 : 6-dihydroxy-2-(*x*-nitro-*p*-tolyl)-5-nitropyrimidine (76%), m. p. 298° (decomp.), which was not obtained analytically pure, although chlorination (see below) yielded a pure dichloro-compound.

4 : 6-Dichloro-2-*p*-ethoxyphenylpyrimidine (3·5 g.) was stirred for 15 minutes with nitric acid (50 c.c.; *d* 1·5) at 20° and then poured on ice. The crude product was filtered off and extracted with boiling light petroleum (b. p. 100—120°). The cooled extracts deposited 4 : 6-*dichloro*-2-(4-*ethoxy*-3-*nitrophenyl*)*pyrimidine* (0·75 g.) which after crystallisation from the same

TABLE 1. 2-*Aryl*-4 : 6-*dichloropyrimidines*.

Aryl	M. p.	Yield, %	Solvent *	Found, % C	H	N	Cl	Formula	Required, % C	H	N	Cl
Ph	96°	77	EtOH	53·1	2·9	11·9	31·1	$C_{10}H_6N_2Cl_2$	53·3	2·7	12·4	31·6
p-MeO·C_6H_4	123—124	67	EtOH	52·0	3·1	11·0	27·2	$C_{11}H_8ON_2Cl_2$	51·8	3·1	11·0	27·8
p-EtO·C_6H_4	98	80	EtOH	54·0	3·6	10·1	26·5	$C_{12}H_{10}ON_2Cl_2$	53·6	3·7	10·4	26·4
β-$C_{10}H_7$	186	58	EtOH	60·6	2·9	9·7	—	$C_{14}H_8N_2Cl_2$	61·1	2·9	10·2	—
5-Nitro-derivatives.												
Ph	168—169	59	Pet	44·5	1·85	15·3	26·1	$C_{10}H_5O_2N_3Cl_2$	44·5	1·85	14·6	26·3
p-C_6H_4Cl †	134—135	40	Pet	40·0	1·4	13·8	34·7	$C_{10}H_4O_2N_3Cl_3$	39·4	1·3	13·4	34·9
4-MeO·C_6H_3·NO_2-3	188—189	53·5	Pet	38·7	2·3	15·9	20·5	$C_{11}H_6O_5N_4Cl_2$	38·3	1·7	16·2	20·6
x-NO_2·C_6H_4Me-*p*	163	61	Pet	40·3	2·0	17·4	21·2	$C_{11}H_6O_4N_4Cl_2$	40·1	1·8	17·0	21·6
4-EtO·C_6H_3·NO_2-3	153—154	53	Pet	—	—	15·2	—	$C_{12}H_8O_5N_4Cl_2$	—	—	15·6	—
β-$C_{10}H_7$	218—219	63	Pet	—	—	13·1	21·4	$C_{14}H_7O_2N_3Cl_2$	—	—	13·1	22·2

* Pet = light petroleum (b. p. 100—120°). † For 2-*p*-chlorophenyl-4 : 6-dihydroxypyrimidine see Moffatt, *J.*, 1950, 1605.

TABLE 2. *Aziridinopyrimidines*.

Substituent* 2	4	5	6	M. p.†	Yield, %	Solvent ‡	Found, % C	H	N	Cl	Formula	Required, % C	H	N	Cl
NH_2	A	NO_2	Me [c]	156° d.	45	M	43·6	4·2	35·9	—	$C_7H_9O_2N_5$	43·1	4·6	35·9	—
A	Me	NO_2	NH_2 [c]	150 d.	45	M	43·3	4·7	35·3	—	$C_7H_9O_2N_5$	43·1	4·6	35·9	—
—	A	NO_2	A [c]	130 d.	69	M	46·4	4·4	—	—	$C_8H_9O_2N_5$	46·4	4·4	—	—
A	A	NO_2 [a]	—	160 d.	46	E	47·0	4·7	—	—	$C_8H_9O_2N_5$	46·4	4·4	—	—
Me	A	NO_2	A [b]	130 d.	62	M	49·0	5·2	31·5	—	$C_9H_{11}O_2N_5$	48·9	5·0	31·7	—
Ph	Cl	—	A	66—67	56	P	61·9	4·1	18·0	15·6	$C_{12}H_{10}N_3Cl$	62·2	4·3	18·1	15·4
(1)	Cl	—	A	169—170	46	P–B	51·2	3·6	19·5	25·7	$C_{12}H_{10}N_4Cl_2$	51·3	3·6	20·0	25·3
p-MeO·C_6H_4	Cl	—	A	132—134	61	E–B	59·9	4·6	16·1	14·0	$C_{13}H_{12}ON_3Cl$	59·7	4·6	16·1	13·7
p-C_6H_4Cl	A	NO_2	A	160 d.	44·5	A	—	—	21·7	10·7	$C_{14}H_{12}O_2N_5Cl$	—	—	22·0	11·2
p-EtO·C_6H_4	Cl	—	A	103—104	66	P	60·9	5·3	—	12·8	$C_{14}H_{14}ON_3Cl$	61·1	5·1	—	12·9
Ph	A	NO_2	A	160 d.	42	E	59·3	4·7	24·6	—	$C_{14}H_{14}O_2N_5$	59·2	4·9	24·7	—
(2)	A	NO_2	A	160 d.	71	A	52·3	4·4	—	—	$C_{15}H_{14}O_4N_6$	52·6	4·1	—	—
(3)	A	NO_2	A	190 d.	78	E	50·1	3·7	—	—	$C_{15}H_{14}O_5N_6$	50·3	3·9	—	—
β-$C_{10}H_7$	Cl	—	A	112—114	84	P	68·4	4·75	15·0	12·8	$C_{16}H_{12}N_3Cl$	68·2	4·3	14·9	12·6
(4)	A	NO_2	A	160 d.	57	E	52·0	4·55	—	—	$C_{16}H_{16}O_5N_6$	51·7	4·3	—	—
β-$C_{10}H_7$	A	NO_2	A	170 d.	41	A	65·3	4·8	—	—	$C_{18}H_{15}O_2N_5$	64·9	4·5	—	—

* A = aziridino; (1) = *p*-chloroanilino; (2) = *x*-nitro-*p*-tolyl; (3) = 4-methoxy-3-nitrophenyl; (4) = 4-ethoxy-3-nitrophenyl.
† Varies with rate of heating; data are for rapid heating; slow heating gives infusible polymers; " d. " = decomp.
‡ M, methanol; E, ethyl acetate; P, light petroleum (b. p. 60—80°); B, benzene; A, acetone.

Prep. of starting materials : [a] Isay, *Ber.*, 1906, **39**, 252; [b] Huber and Hölscher, *Ber.*, 1938, **71**, 87; [c] Boon, Jones, and Ramage, *J.*, 1951, 96.

solvent had m. p. 118° (Found : C, 45·8; H, 2·9; N, 13·05; Cl, 21·9. $C_{12}H_9O_3N_3Cl_2$ requires C, 45·9; H, 2·9; N, 13·35; Cl, 22·6%).

Chlorination.—This was effected by treatment of the appropriate 4 : 6-dihydroxypyrimidine (1 part) with dimethylaniline (1 part) and phosphoryl chloride (5 parts) under reflux for 1 hour. The excess of phosphoryl chloride was distilled off under reduced pressure and the residue triturated with ice; recrystallisation was from ethanol or light petroleum (b. p. 100—120°) as indicated in Table 1 where the properties of the *products* are summarised.

Reaction of Chloropyrimidines with Ethyleneimine.—To a solution of ethyleneimine (2·1 mols.) and triethylamine (2·2 mols.) in dry benzene was added, with stirring and cooling, a solution of the appropriate chloropyrimidine (1·0 mol.) in benzene; or, in the cases of relatively insoluble compounds, the finely ground solid was added; the temperature was kept at 35—45°. Stirring was then continued at this temperature for a further hour, with gentle heating as the exothermic reaction slackened. The mixture was filtered from triethylamine hydrochloride, the filtrate evaporated at $\not>40°$ under reduced pressure, and the residue recrystallised as indicated in Table 2. A certain amount of the less soluble products was filtered off with the triethylamine hydrochloride and was recovered by leaching the latter with water. In the case of the unnitrated 4 : 6-dichloropyrimidines only one chlorine atom was replaced by this procedure. Both chlorine atoms of compounds having in addition a 5-nitro-group were replaced. The characteristics of the products obtained are summarised in Table 2.

Reaction of 4 : 6-*Dichloro-2-phenylpyrimidine with Lithioethyleneimine.*—Lithium (1·4 g., 0·2 atom), in small pieces, was stirred in sodium-dried ether (30 c.c.) in an atmosphere of dry nitrogen while methyl iodide (14·2 g., 0·1 mol.) was added in dry ether (30 c.c.) during 0·5 hour. The reaction was moderated as necessary by cooling. Stirring under nitrogen was continued for a further 0·5 hour, by which time the reaction had ceased, although small fragments of lithium remained. Ethyleneimine (3·65 c.c., 0·07 mol.) in dry ether (30 c.c.) was added to the stirred mixture during 0·5 hour, and after a further 0·5 hour's stirring 4 : 6-dichloro-2-phenylpyrimidine (4·5 g., 0·02 mol.) in ether (50 c.c.) was added with gentle boiling. Refluxing was continued for a further hour, the solution then filtered from residual lithium through 100-mesh gauze, and the filtrate decomposed with ice and water (100 c.c.). The ethereal layer was separated and the aqueous layer twice extracted with further quantities of ether. The combined extracts were dried (Na_2SO_4) and evaporated, to yield crude 4 : 6-*diaziridino-2-phenylpyrimidine* which recrystallised from light petroleum (b. p. 60—80°) as colourless needles, m. p. 111—112° (1·8 g., 38%) (Found : C, 70·0; H, 6·15; N, 23·35. $C_{14}H_{14}N_4$ requires C, 70·6; H, 5·9; N, 23·5%). Similarly prepared was 4 : 6-*diaziridino-2-β-naphthylpyrimidine* (41%), m. p. 156—158° with polymerisation (Found : C, 14·6; H, 5·4; N, 19·7. $C_{18}H_{16}N_4$ requires C, 75·0; H, 5·6; N, 19·4%).

5-*Amino-*4 : 6-*diaziridino-2-phenylpyrimidine.*—4 : 6-Diaziridino-5-nitro-2-phenylpyrimidine (3·0 g.) in benzene (40 c.c.)–methanol (40 c.c.) was shaken with hydrogen over Raney nickel. Uptake was 723 c.c. (theor., 765 c.c. at 20°); the reaction mixture was filtered and evaporated below 40° to a red solid which was recrystallised repeatedly from acetone (carbon) and yielded 5-*amino-*4 : 6-*diaziridino-3-phenylpyrimidine* (0·8 g.) as a pale yellow microcrystalline powder, m. p. 147—148° (Found : N, 27·4. $C_{14}H_{15}N_5$ requires N, 27·7%).

Oxidation of 4 : 6-*Dihydroxy-2-(4-methoxy-3-nitrophenyl)-5-nitropyrimidine.*—The pyrimidine (5 g.) was dissolved in a solution of sodium hydroxide (1·3 g., 2·0 mols.) in hot water (100 c.c.), and hot 10% aqueous potassium permanganate was added at 80° during 0·5 hour. When about 120 c.c. had been added a permanent purple colour resulted; the reaction mixture was kept at 80° for a further 45 minutes and filtered hot from manganese salts. The filtrate was acidified with sulphuric acid and crude 4-methoxy-3-nitrobenzoic acid separated. The crude acid (0·92 g.), after several crystallisations from aqueous methanol, had m. p. 185—186° alone or mixed with an authentic sample. The product was further characterised as the methyl ester, m. p. 108°. Similar oxidation of 4 : 6-dihydroxy-5-nitro-2-phenylpyrimidine yielded benzoic acid identified by m. p. and mixed m. p.

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