NOVEL PYRIMIDINE DERIVATIVES, REACTIONS AND ULTRAVIOLET SPECTRA*

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Conditions for a selective hydrolysis of 5-(dimethylaminomethyleneamino)pyrimidines *I* to 5-N-formylaminopyrimidines *II* and 5-aminopyrimidines *III* have been determined. In this connection, 5-aminopyrimidine-2-carboxylic acid (*IIIp*) has been obtained. The UV spectra of a series of 2,5-substituted pyrimidines were taken.

A simple synthesis of some 5-(dimethylaminomethyleneamino) substituted pyrimidines has been recently reported[1]. It has now appeared desirable to determine conditions of a selective hydrolysis of these substances to the corresponding 5-N-formylamino and 5-amino derivatives. Included are also derivatives obtained[2] during investigations on diazotisation of 2-amino-5-(dimethylaminomethyleneamino)pyrimidine (*Ia*). The dimethylaminomethyleneamino group attached to the pyrimidine nucleus represents a special case of a N,N,N'-trisubstituted base of the general formula $R^1N{=}CH{-}NR^2R^3$ (*IV*) but, from the synthetic standpoint, it may also be regarded as an advantageously protected amino group. This grouping has been virtually utilised in blocking of the pyrimidine and purine amino groups for purposes of the oligonucleotide synthesis[3]. In this connection, recovery of the free amino group has been examined under hydrolytical conditions, but the intermediary N-formyl derivatives have not been observed[3]. Some general aspects of the hydrolysis of formamidines have been investigated by DeWolfe with the use of symmetrical N,N'-diarylformamidines as model compounds[4].

Contrary to the above mentioned kinetic investigations on hydrolysis of the formamidine function, we were particularly interested in isolation of the intermediary N-formylamino derivatives *II*. The hydrolysis of 2-substituted 5-(dimethylaminomethyleneamino)pyrimidines *I* was therefore studied in aqueous media of a wide pH range and the reaction course was examined by thin-layer chromatography. In acidic media, the primary formation of the N-formylamino derivatives *II* was observed

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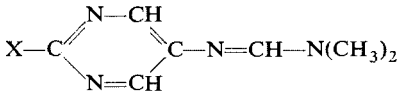
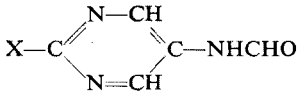
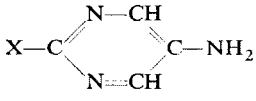


I



II



III

a, X = NH_2	*e*, X = OCH_3	*i*, X = F	*m*, X = SO_2CH_3
b, X = $N(CH_3)_2$	*f*, X = SH	*j*, X = Cl	*n*, X = CN
c, X = OH	*g*, X = SCH_3	*k*, X = Br	*o*, X = $CONH_2$
d, X = $OCOCH_3$	*h*, X = H	*l*, X = $SOCH_3$	*p*, X = COOH

with all the compounds of type *I*. In mildly acidic media such as 0·2M acetic acid or 0·02M sulfuric acid, the product of a partial hydrolysis resulted, namely, the N-formylaminopyrimidine derivative *II*. Under conditions of an alkaline hydrolysis however, formation of the N-formyl derivatives *II* is accompanied by a complete saponification to the amino compounds *III*. The direct conversion of compounds *I* to the amino derivatives *III* may be advantageously accomplished with 0·2M sulfuric acid or 5% aqueous potassium carbonate.

The 2,5-diaminopyrimidine (*IIIa*) obtained from compound *Ia* by alkaline hydrolysis was in turn transformed to the bis-acetyl derivative *V* on treatment with acetic anhydride. Under the above conditions, the hydrolysis of the hydroxy and mercapto derivatives *Ic* and *If* afforded exclusively the corresponding N-formylaminopyrimidines *IIc* and *IIf*, resp. The attempted complete hydrolysis to the aminopyrimidines *IIIc* and *IIIf*, resp., failed because of the decomposition of the substrate.

In the series of 2-substituted 5-(dimethylaminomethyleneamino)pyrimidines *I*, some substituents X are susceptible to hydrolysis, particularly the halo atoms (especially the fluoro substituent) and the methylsulfonyl group. The replacement rate of these substituents with the formation of hydroxy compounds increases with the increasing concentration of hydroxylic ions, *i.e.*, with the increasing pH value. In weakly acidic media, the incorporation of the hydroxylic function is considerably slower than the hydrolytic reaction proceeding on the other end of the molecule and may be thus suppressed to minimum by a suitable choice of reaction conditions (0·2M acetic acid).

From the whole series, the hydrolysis of the fluoropyrimidine derivative *Ii* is the most problematic. A successful conversion of compound *Ii* to the N-formylamino derivative *IIi* or the amino derivative *IIIi* was finally accomplished by the action of aqueous potassium hydrogen fluoride at the appropriate temperature. When the hydrolysis is performed in alkaline media, the dimethylaminomethyleneamino group is degraded to the free dimethylamine, a strong nucleophile, which is also capable

of attacking the position 2 of the pyrimidine nucleus. Thus *e.g.*, the attempted hydrolysis of 5-(dimethylaminomethylene amino)-2-fluoropyrimidine (*Ii*) with aqueous potassium carbonate afforded a high yield (87%) of 5-amino-2-dimethylaminopyrimidine (*IIIb*) though the dimethylamine may be present in the reaction mixture in the maximum amount of one equivalent when a 100% conversion of dimethylaminomethyleneamino group to the N-formylamino group is assumed.

TABLE I

UV Spectra of Compounds *I*, *II*, and *III*; λ_{max} (log ε)

Note	Substituent	*I*	*II*	*III*
a	NH_2	273 (4·28)	256 (4·20)	244 (4·12)
		337 (3·41)	322 (3·31)	346 (3·35)
b	$N(CH_3)_2$	—	—	256 (4·29)
				360 (3·40)
c	OH	271 (4·27)	248 (3·90)	—
		357 (3·43)	337 (3·07)	
d	$OCOCH_3$	277 (4·20)	—	—
e	OCH_3	213 (3·72)	244 (4·10)	237 (3·97)
		269 (4·21)	299 (3·40)	327 (3·39)
		316 (3·46)[a]		
f	SH[b]	216 (3·96)	302[c]	—
		302 (4·36)	355[c]	—
		366 (3·20)		
g	SCH_3	286 (4·42)	273 (4·29)	264 (4·25)
				343 (3·30)
h	H	278 (3·50)	241 (4·08)	246 (3·98)
			273 (3·48)[a]	313 (3·46)
i	F	270 (4·22)	236 (4·01)	235 (4·02)
			283 (3·38)	327 (3·45)
j	Cl	283 (4·26)	246 (4·10)	252 (4·11)
				326 (3·40)
k	Br	285 (4·30)	249 (4·05)	254 (4·11)
				327 (3·35)
l	$SOCH_3$	296 (4·41)	—	—
m	SO_2CH_3	298 (4·30)	258 (4·23)	271 (4·27)
				307 (3·55)[a]
n	CN	224 (3·68)[a]	268 (4·14)	282 (4·25)
		325 (4·33)		
o	$CONH_2$	—	—	283 (4·14)
p	COOH	—	—	286 (4·07)

[a] Inflex; [b] measured in water; [c] in view of the low solubility of the substance, the ε value was not determined.

Some substituents X may under special hydrolytical conditions undergo additional transformations. Thus in strongly alkaline media, the nitrile *In* is transformed to the amide *IIIo* and then to 5-aminopyrimidine-2-carboxylic acid (*IIIp*), the pyrimidine analogue of 4-aminobenzoic acid. Under milder hydrolytical conditions however, the two reacting groups are different enough and we obtain the expected compounds *IIn* or *IIIn*. The behaviour of the acetoxy derivative *Id* is quite opposite. Thus, 5-(dimethylaminomethyleneamino)-2-hydroxypyrimidine (*Ic*) is obtained even by the action of atmospheric moisture; it was not possible to saponify the formamidine function without affecting the ester bond.

The ultraviolet spectra of a series of novel 2,5-substituted pyrimidine derivatives reported in the present work and two earlier papers[1,2] are shown in Table I. The corresponding infrared spectra will be discussed elsewhere.

TABLE II

2-Substituted 5-N-Formylaminopyrimidines

Compound Substituent	Method	M.p., °C (solvent)	Yield %	Formula (m.w.)	Calculated/Found			
					% C	% H	% N	% X
IIa	*Aa*	221–221·5	84	$C_5H_6N_4$	43·5	4·4	40·6	—
NH_2		(ethanol)		(138·1)	43·7	4·5	40·4	—
IIc	*Aa*	>360	72	$C_5H_5N_3O_2$	43·2	3·6	30·2	—
OH		(water)		(139·1)	43·3	3·5	30·4	—
IIe	*Aa*	181·5–182	85	$C_6H_7N_3O_2$	47·1	4·6	27·4	—
OCH_3		(water)		(153·1)	47·1	4·7	27·7	—
IIf	*Aa*	295–298[a]	70	$C_5H_5N_3OS$	38·7	3·3	27·1	20·7[b]
SH		(precipitate)		(155·2)	38·3	3·5	26·8	20·3
IIg	*Aa*	122–123	89	$C_6H_7N_3OS$	42·6	4·2	24·8	18·9[b]
SCH_3		(water)		(169·1)	41·8	4·1	24·8	18·5
IIh	*Bb*	186–187	81	$C_5H_5N_3O$	48·8	4·1	34·1	—
H		(ethanol)		(123·1)	48·7	4·1	33·8	—
IIj	*Bb*	120–122	86	$C_5H_4ClN_3O$	38·1	2·6	26·7	22·5[c]
Cl		(benzene)		(157·6)	38·3	2·7	26·7	22·4
IIk	*Bb*	130–131	87	$C_5H_4BrN_3O$	29·7	2·0	20·8	39·6[d]
Br		(benzene)		(202·0)	29·6	2·0	21·0	39·8
IIm	*Ba*	161–162	79	$C_6H_7N_3O_3S$	35·8	3·5	20·9	15·9[b]
SO_2CH_3		(ethanol)		(201·2)	35·9	3·6	21·2	15·8
IIn	*Bb*	192–193	84	$C_6H_4N_4O$	48·6	2·7	37·8	—
CN		(ethanol)		(148·1)	48·2	2·7	37·1	—

[a] Decomposition; [b] % S; [c] % Cl; [d] % Br.

EXPERIMENTAL

Melting points were taken on a heated microscope stage (Kofler block). The UV spectra were recorded on an Optica Milano CF 4 apparatus. Mass spectra were measured on a double focal AEI MS-902 apparatus.

2-Substituted 5-N-Formylaminopyrimidines *II*

The 2-substituted 5-(dimethylaminomethyleneamino)pyrimidine[1,2] *I* (0·001 mol) was dissolved in *A*) 0·02M sulfuric acid or *B*) 0·2M acetic acid (10 ml each) and the solution stirred at 100°C for 1 h. The hydrolytical product was isolated by two procedures: *a*) the reaction mixture was cautiously concentrated to a small volume, the concentrate cooled down to 0°, the solid collected with suction, dried, and crystallised; *b*) the reaction mixture was treated with saturated aqueous potassium carbonate (20 ml), extracted with two 20 ml portions of dichloromethane, the extracts combined, dried over calcinated potassium carbonate, evaporated, and the residues crystallised. For analyses and properties of compounds *II* and preparative methods see Table II.

2-Substituted 5-Aminopyrimidines *III*

A. Compound[1,2] *I* (0·01 mol) was dissolved in 5% aqueous potassium carbonate (20 ml), the solution heated at 100°C for 1 h, cooled down, the dimethylamine removed, and the remaining

TABLE III

2-Substituted 5-Aminopyrimidines

Compound Substituent	Method (min)	M.p., °C (solvent)	Yield %	Formula (m.w.)	Calculated/Found % C	% H	% N	% X
IIIa	*A*	212–213[a]	85	$C_4H_6N_4$	44·1	5·7	51·2	—
NH_2		(ethanol)		(110·1)	43·6	5·5	50·9	—
IIIe	*A*	119–120	86	$C_5H_7N_3O$	48·0	5·6	33·6	—
OCH_3		(benzene)		(125·1)	48·3	5·6	33·0	—
IIIg	*A*	110–110·5[b]	85	$C_5H_7N_3S$	42·6	5·0	29·7	22·7[c]
SCH_3		(water)		(141·2)	42·4	5·0	29·2	22·9
IIIh	*A*	171–172[d]	77	$C_4H_5N_3$	50·5	5·3	44·2	—
H		(benzene)		(95·1)	50·9	5·3	44·0	—
IIIj	*Bb*	196–198[e]	87	$C_4H_4ClN_3$	37·1	3·1	32·4	27·4[f]
Cl	(75)	(water)		(129·6)	37·4	3·2	32·5	27·1
IIIk	*Bb*	182–183	77	$C_4H_4BrN_3$	27·6	2·3	24·2	45·9[g]
Br	(60)	(benzene)		(174·0)	27·9	2·4	24·7	45·5
IIIm	*Ba*	140–141	81	$C_5H_7N_3O_2S$	34·7	4·1	24·3	18·5[c]
SO_2CH_3	(30)	(ethanol)		(173·2)	34·8	4·2	24·3	18·4
IIIn	*Bb*	230–231	86	$C_5H_4N_4$	50·0	3·4	46·6	—
CN	(30)	(ethanol)		(120·1)	50·3	3·4	46·3	—

[a] Reported[5], m.p. 213°C; [b] reported[7], m.p. 105°C; [c] % S; [d] reported[6], m.p. 170–171°C; [e] reported[6], m.p. 198–199°C; [f] % Cl; [g] % Br.

mixture concentrated to a small volume under diminished pressure. The concentrate was cooled down to 0°C to deposit a solid which was collected with suction, washed with a little ice-cold water, dried, and crystallised.

B. A solution of compound[1,2] *I* (0·01 mol) in 0·2M sulfuric acid (10 ml) was heated at 110°C for the periods of time given in Table III. The product was isolated by two procedures: *a*) the mixture was concentrated under diminished pressure to a small volume, the concentrate cooled down to 0°C, the product *III* collected with suction, washed with a little ice-cold water, dried, and crystallised; *b*) the cold mixture was made alkaline with excess saturated aqueous potassium carbonate, extracted with two 20 ml portions of dichloromethane, the extracts combined, dried, evaporated and the residual aminopyrimidines *III* crystallised. For preparative methods, properties, and analyses see Table III.

2-Fluoro-5-N-formylaminopyrimidine (*IIi*)

Compound[2] *Ii* (0·17 g; 0·001 mol) was dissolved in 3M potassium hydrogen fluoride (10 ml), the solution heated at 75°C for 75 min, cooled down, made alkaline with saturated aqueous potassium carbonate (20 ml), and extracted with two 20 ml portions of dichloromethane. The extracts were combined, dried over calcinated potassium carbonate, and evaporated to afford 0·12 g (85%) of compound *IIi*, m.p. 95—100°C; after crystallisation from benzene, m.p. 116 to 118°C. For $C_5H_4FN_3O$ (141·1) calculated: 42·6% C, 2·9% H, 13·5% F, 29·8% N; found: 43·4% C, 3·1% H, 13·3% F, 30·4% N.

5-Amino-2-fluoropyrimidine (*IIIi*)

Compound[2] *Ii* (0·17 g; 0·001 mol) was dissolved in 3M aqueous potassium hydrogen fluoride (10 ml), the solution heated at 120°C (bath temperature) for 75 min, cooled down, made alkaline with saturated aqueous potassium carbonate (20 ml), and extracted with two 20 ml portions of dichloromethane. The extracts were combined, dried over calcinated potassium carbonate, and evaporated to afford 0·99 g (80%) of compound *IIIi*, m.p. 150—160°C; after crystallisation from benzene, m.p. 178—179°C. For $C_4H_4FN_3$ (113·1) calculated: 42·5% C, 3·6% H, 16·8% F, 37·2% N; found: 42·6% C, 3·6% H, 16·7% F, 37·5% N.

5-(Dimethylaminomethyleneamino)-2-hydroxypyrimidine (*Ic*)

A solution of compound[2] *Id* (0·2 g; 0·001 mol) in methanol (5 ml) was treated with 2M methanolic sodium methoxide (1 ml), the mixture stirred at room temperature for 15 min, neutralised with methanolic hydrogen chloride, evaporated, the residue extracted with dichloromethane, and the extract evaporated to afford 0·14 g (84%) of compound *Ic*, m.p. 200—207°C; after crystalliastion from ethanol, m.p. 206—208°C. For $C_7H_{10}N_4O$ (166·2) calculated: 50·6% C, 6·1% H, 33·7% N; found: 49·8% C, 6·1% H, 33·6% N.

5-Amino-2-carbamoylpyrimidine (*IIIo*)

A mixture of compound[1] *In* (0·175 g; 0·001 mol) and 0·2M sodium hydroxide (1 ml) was heated at 100°C for 1 h, cooled down, the solid collected with suction, washed with a little ice-cold water, and dried to afford 0·125 g (90%) of compound *IIIo*, m.p. 220—232°C. The analytical sample, m.p. 233—235°C (water). For $C_5H_6N_4O$ (138·1) calculated: 43·5% C, 4·4% H, 40·6% N; found: 43·4% C, 4·3% H, 40·6% N.

5-Aminopyrimidine-2-carboxylic Acid (*IIIp*)

A mixture of compound[1] *In* (0·35 g; 0·002 mol) and 2M sodium hydroxide (4 ml) was heated at 100°C for 20 min, cooled down, and neutralised with conc. perchloric acid. The precipitate was collected with suction, washed with a little ice-cold water, and dried to afford 0·22 g (79%) of the acid *IIIp*, 245—260°C. The analytical product, m.p. 270—274°C (water; decomp.). For $C_5H_5N_3O_2$ (139·1) calculated: 43·2% C, 3·6% H, 30·2% N; found: 43·1% C, 3·6% H, 29·8% N.

5-Amino-2-dimethylaminopyrimidine (*IIIb*)

A mixture of compound[2] *Ii* (0·17 g; 0·001 mol) and 5% aqeuous potassium carbonate (4 ml) was heated at 110°C for 45 min, cooled down, extracted with two 20 ml portions of dichloromethane, the extracts combined, dried over anhydrous potassium carbonate, and evaporated to afford 0·12 g (87%) of compound *IIIb*, m.p. 80—84°C. For the analysis, a sample was sublimed at 100°C/0·3 Torr; m.p. 83·0—83·5°C. For $C_6H_{10}N_4$ (138·2) calculated: 52·1% C, 7·3% H, 40·6% N; found: 51·7% C, 7·2% H, 41·2% N.

2,5-Bis(acetamino)pyrimidine (*V*)

A mixture of 2,5-diaminopyrimidine (*IIIa*; 0·22 g; 0·001 mol) and acetic anhydride (1 ml) was heated at 100°C for 10 min, cooled down, the solid collected with suction, and washed with ethanol to afford 0·35 g (90%) of compound *V*, m.p. 285—290°C. The analytical sample, m.p. 294—195°C (ethanol). For $C_8H_{10}N_4O_2$ (194·2) calculated: 49·5% C, 5·2% H, 28·8% N; found: 49·6% C, 5·1% H, 28·3% N.

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