DIAZOTISATION OF THE AMINO GROUP ON THE PYRIMIDINE NUCLEUS*

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The conversion of 2-amino-5-(dimethylaminomethyleneamino)pyrimidine (*Ia*) to the corresponding halo derivatives by diazotisation in the presence of halide ions has been examined. In the reaction of 2-substituted 5-amino derivatives *III* with nitrous acid, an isomerisation has been observed with the formation of pyrimidines substituted at position 4 by a hydroxylic group.

Earlier investigations[1] made accessible a series of 2,5-substituted pyrimidines, *inter alia* 2-amino-5-(dimethylaminomethyleneamino)pyrimidine (*Ia*). In the present paper we wish to report the reaction of nitrous acid with the amino group at position 2 of compounds *Ia* and *IIa* as well as with the amino group at position 5 of compounds *III* obtained on hydrolysis of the corresponding 2-substituted 5-(dimethylaminomethyleneamino)pyrimidines[2]. Reactions of nitrous acid with amino compounds of the pyrimidine series have not been as widely utilised as in the aromatic series. The amino groups at positions 2, 4 or 6 of the pyrimidine ring may be transformed to hydroxylic functions by reaction with nitrous acid in an aqueous medium. In these reactions, unstable diazonium salts are assumed as intermediates which are immediately decomposed with the simultaneous liberation of nitrogen. The structure of products depends on nucleophiles which are present in the reaction mixture. Thus in the presence of halide ions, the diazotisation of the amino group results in its replacement by the corresponding halo atom but the yields are not usually high[3].

In connection with inyestigations on the reactivity of derivatives *Ia* and *IIa* it appeared of interest to find conditions which would lead to higher yields of the halo derivatives than reported in analogous cases. The following ideas were taken into consideration. *a*) An increased concentration of the corresponding halide ion should lead to an increased yield of the product. *b*) Each product should require an appropriate optimum acidity of the reaction mixture. *c*) Side reactions should be suppressed, such as the formation of a hydroxy derivative by a direct decomposition of the diazonium salt, liberation of bromine by the action of nitrous acid in the synthesis of bromo derivatives and the like.

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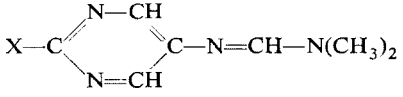
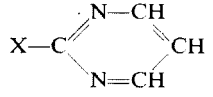
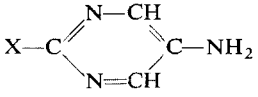
The concentrated hydrochloric acid has been so far the single medium for conversion of aminopyrimidines to the corresponding chloro derivatives through diazotisation[3,4]. In our experiments, various conditions were used for this conversion taking particularly into account the points *a*) and *b*) mentioned above. In this manner, the yields of the examined reactions were considerably increased. Thus, a 5M solution of lithium chloride in 4M hydrochloric acid proved to be the medium of choice. The acidity of this medium makes possible a sufficiently rapid diazotisation and lithium chloride guarantees for a sufficient concentration of chloride ions. While the diazotisation of 2-aminopyrimidine (*IIa*) in concentrated hydrochloric acid affords a 26–27% yield of 2-chloropyrimidine (*IIb*), an improved yield of 50% is obtained in the mixture of hydrochloric acid and lithium chloride. A similar improvement has been encountered in the transformation of 2-amino-5-(dimethylaminomethyleneamino)pyrimidine (*Ia*) into the chloro derivative *Ib*: in conc. hydrochloric acid, the yield was 30% and in hydrochloric acid–lithium chloride the yield was raised to 60%. The preparation of the bromo derivative is complicated by the concomitant oxidation of bromide ions to elemental bromine by the action of nitrous acid. When



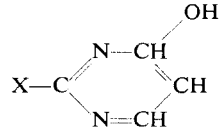
Ia; X = NH_2 *Id*; X = F
Ib; X = Cl *Ie*; X = $OCOCH_3$
Ic; X = Br



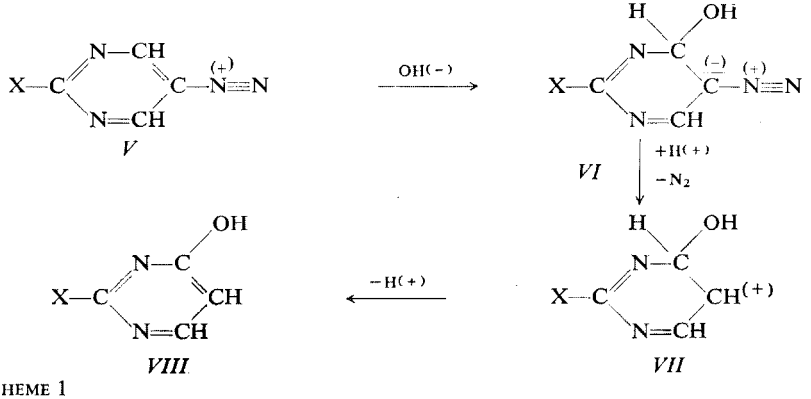
IIa; X = NH_2 *IId*; X = F
IIb; X = Cl *IIe*; X = $OCOCH_3$
IIc; X = Br



IIIa; X = NH_2 *IIIc*; X = SO_2CH_3
IIIb; X = SCH_3 *IIId*; X = H



IVa; X = NH_2
IVb; X = SCH_3
IVc; X = OH



SCHEME 1

the substrate is not sensitive to bromine, this interfering oxidation may be suppressed by the addition of elemental bromine into the reaction mixture[5]. A more general technique consists in a very slow addition of hydrobromic acid in the course of the reaction[6,7]; also this procedure is not quite satisfactory. We have now observed that the undesired oxidation of bromide ions may be almost completely suppressed when the diazotisation is performed in aqueous acetic acid (25%) saturated with an alkali metal bromide. By this process, 2-aminopyrimidine affords the 2-bromo derivative *IIc* in 31% yield (the highest reported[6] yield, 27%) and 2-bromo-5-(dimethylaminomethyleneamino)pyrimidine (*Ic*) is obtained in 48% yield.

Conditions for the formation of fluorinated pyrimidines by the diazotisation process are not favourable particularly because of the low nucleophilicity if the fluoride anion. The classical Baltz–Schiemann method based on isolation of the diazonium salt in the form of the tetrafluoroborate and its subsequent decomposition cannot be used in the pyrimidine series because of the extreme instability of diazonium salts derived from pyrimidines. A single preparation of a fluorinated pyrimidine by the diazotisation process has been reported in the literature[8], namely, of 2-fluoropyrimidine from 2-ami-

TABLE I
Compounds *Ib*—*Ie* and *IIb*—*IIe*

Compound Substituent	$NaNO_2$ mol yield, %	M.p. °C[a]	Formula (m.wt.)	Calculated/Found			
				% C	% H	% N	% Hal
Ib	2·0	102—103	$C_7H_9ClN_4$	45·5	4·9	30·4	19·2
Cl	60		(184·6)	45·5	5·0	30·4	19·4
Ic	2·0	96—97	$C_7H_9BrN_4$	36·7	4·0	24·5	34·9
Br	48		(229·1)	37·0	4·0	25·0	34·8
Id	1·3	96—97	$C_7H_9FN_4$	50·0	5·4	33·3	11·3
F	60		(168·2)	50·5	5·2	33·5	11·5
Ie	4·0	102—103	$C_9H_{12}N_4O_2$	51·9	5·8	26·9	—
$OCOCH_3$	90		(208·2)	51·6	5·8	27·0	—
IIb	4·0	65—66[b]	$C_4H_3ClN_2$	41·9	2·6	24·5	31·0
Cl	50		(114·6)	42·1	2·7	24·3	30·8
IIc	3·0	56—57[c]	$C_4H_3BrN_2$	30·2	1·9	17·6	50·2
Br	31		(159·0)	30·3	2·0	17·3	49·5
IId	2·0	17—18[d]	$C_4H_3FN_2$	49·0	3·1	28·5	19·4
F	25		(98·2)	49·2	3·2	28·7	19·3
IIe	4·0	75—80/	$C_6H_6N_2O_2$	52·2	4·4	20·3	—
$OCOCH_3$	60	0·4 Torr	(138·1)	52·0	4·0	20·0	—

[a] Crystallised from cyclohexane; [b] reported[4], m.p. 64·5—65·5°C; [c] reported[6], m.p. 55·5—57·0°C; [d] purified by preparative gas chromatography.

nopyrimidine by diazotisation in fluoroboric acid. By a similar technique some 6,9-substituted 2-fluoropurines have been obtained in unsatisfactory yields[9]. We have now prepared 2-fluoropyrimidine (*IId*) and 5-(dimethylaminomethyleneamino)-2-fluoropyrimidine (*Id*) in 20% and 60% yields, resp., by diazotisation of the corresponding amines *IIa* and *Ia* in hydrofluoric acid. The isolation of 2-fluoropyrimidine is rather difficult (volatility) and was accomplished by preparative gas chromatography. A mixture of hydrofluoric acid and fluoroboric acid affords similar yields while in fluoroboric acid alone, the yields of the fluoropyrimidines *IId* and *Id* are lower (15% and 30%, resp.). Of a general interest may be regarded the result of the diazotisation of 2-amino-5-(dimethylaminomethyleneamino)pyrimidine (*Ia*) in aqueous acetic acid in the presence of an equivalent amount of the fluoride, chloride, and bromide ions since only the bromo derivative *Ic* was isolated from the reaction mixture while the chloro derivative *Ib*, the fluoro derivative *Id* or the acetoxy derivative *Ie* were absent as shown by thin-layer chromatography. It may be inferred from this observation that the reaction course is dependent on the anions present, particularly on their nucleophilic character.

In glacial acetic acid, the reaction of 2-aminopyrimidines *Ia* and *IIa* with nitrous acid was also of interest affording 2-acetoxy-5-(dimethylaminomethyleneamino)pyrimidine (*Ie*) in 90% yield and the corresponding 2-acetoxy derivative *IIe* (60%). The lower yield of compound *IIe* may be ascribed to its unstability and susceptibility to atmospheric moisture (probably hydrolysis to 2-hydroxypyrimidine).

Attention has also been paid to reactions of nitrous acid with pyrimidine derivatives *III*, substituted at position 5 by an amino group. As shown by previous experiments, the diazotisation of the amino group at position 5 of the pyrimidine ring is successful in those cases when both the vicinal positions 4 and 6 are substituted (thus, *e.g.*, a relatively stable diazonium salt may be obtained from 2,5-diamino-4,6-dimethylpyrimidine[10]) or when at least one of these positions is occupied by a group of a favourable effect on the course of the diazotisation (as exemplified by conversion of 5-aminouracil to the so called diazouracil[11]). On the other hand, isolation of any products from the diazotisation of 5-aminopyrimidine completely failed[12] (see also ref.[13]). The attempted treatment of 5-aminopyrimidines *IIIa*–*IIId* with nitrous acid in an aqueous mineral acid did not afford any individual product. When the diazotisation was performed in concentrated sulfuric acid, there were isolated in a low yield products, the analysis of which indicated replacement of the amino group by a hydroxylic group with compounds *IIIa*, *IIIb*, and *IIIc* and moreover, in the case of compound *IIIc*, an additional replacement of the methylsulfonyl group by a further hydroxylic group. These products were then unexpectedly identified as the 4-hydroxy derivatives *IV*, namely, isocytosine (2-amino-4-hydroxypyrimidine, *IVa*), 4-hydroxy-2-methylthiopyrimidine (*IVb*), and uracil (*IVc*).

For this isomerisation, we did not find in the literature any direct analogy. The most probable explanation is shown on Scheme 1. Positions 4 and 6 of the pyrimidine ring

are readily susceptible to the nucleophilic substitution. The diazonium group belongs to substituents with the strongest effect inducing a positive charge at *ortho* and *para* positions of the aromatic ring (its σ_p is[14] +1·8). In the cation *V*, both the effects are cooperative and produce extremely favourable conditions for a nucleophilic attack at positions 4 and 6. The hydroxylic group (or another group transformable into the hydroxylic group in the further course of the reaction) attacks the thus-activated position 4 with the formation of the intermediate *VI*. This species may react analogously to alicyclic diazo compounds and lose after protonation a nitrogen molecule (step *VII*). The final product may be then formed by a direct loss of the proton. The involvement of 4,5-dihydro-4,5-dihydroxypyrimidine as intermediate cannot be excluded. The replacement of the methylsulfonyl group in compound *IIIc* by a hydroxylic group during the diazotisation process, is obviously accomplished also at the stage of the diazonium salt. Analogous transformations have been reported[12].

The attempted isolation of some product from the diazotisation of 5-aminopyrimidine under the above mentioned conditions failed. In this case, a hydrolytical destruction of the pyrimidine nucleus obviously takes place since the reaction mixture does not contain any material absorbing in the UV region. A plausible explanation might consist in similarity between the pyrimidine-5-diazonium ion (*V*, X = H) and the unsubstituted 1,3,5-triazine which is known to undergo a very rapid hydrolytical decomposition in aqueous media[15].

EXPERIMENTAL

Melting points were taken on a heated microscope stage (Kofler block). Mass spectra were recorded on a double focal AEI MS-902 apparatus. Substance *IIIc* was isolated by preparative gas chromatography on a Fractovap P apparatus (Carlo Erba).

Preparation of Chloro Derivatives *Ib* and *IIb*

Compound (0·001 mol) *Ia* (ref.[1]) or *IIa* (ref.[16]) was dissolved in a solution (5 ml) of 5M lithium chloride in 4M hydrochloric acid and then treated portionwise over 30 min at −15°C with excess solid sodium nitrite (see Table I) under efficient stirring. The resulting mixture was stirred at 0°C for additional 30 min, diluted with dichloromethane (30 ml), and made alkaline with excess saturated aqueous potassium carbonate. The dichloromethane layer was separated, dried, and evaporated (because of the volatility of 2-chloropyrimidine *IIb*, the dichloromethane must be removed very cautiously). The residue is then crystallised from cyclohexane. For properties and analyses of compounds *Ib* and *IIb* see Table I.

Bromo Derivatives *Ic* and *IIc*

Compound (0·001 mol) *Ia* (ref.[1]) or *IIa* (ref.[16]) was dissolved in 6 ml of 25% aqueous acetic acid previously saturated with sodium bromide and the solution was treated portionwise over 30 min at 15−20°C with excess solid sodium nitrite (Table I). The stirring was continued for 15 min, the mixture diluted with dichloromethane (30 ml), cooled down to 0°C, made alkaline with saturated aqueous potassium carbonate, the methylene chloride layer separated, dried, and evaporated. The products *Ic* and *IIc* were crystallised from cyclohexane.

Fluoro Derivatives *Id* and *IId*

Compound (0·001 mol) *Ia* (ref.[1]) or *IIa* (ref.[16]) was dissolved in 40% aqueous hydrofluoric acid (7 ml) and the solution treated portionwise with stirring at 0°C over 30 min with solid sodium nitrite (Table I). The mixture was then stirred for additional 15 min, diluted with dichloromethane (30 ml), made alkaline with saturated aqueous potassium carbonate, the organic layer separated, dried, and evaporated; in the case of 2-fluoropyrimidine (*IId*) which is volatile, the solvent was removed by distillation at ordinary pressure through a column and the residue was subjected to preparative gas chromatography (4% Carbowax 20 M, at 135°C).

Acetoxy Derivatives *Ie* and *IIe*

Compound (0·001 mol) *Ia* (ref.[1]) or *IIa* (ref.[16]) was dissolved in glacial acetic acid (3 ml) and the solution treated portionwise over 30 min at 15°C with solid sodium nitrite (Table I). The stirring was continued for 15 min, the mixture cooled down to 0°C, diluted with dichloromethane (30 ml), and processed similarly to preceding paragraphs.

Attempted Diazotisation of 5-Aminopyrimidines *IIIa*—*IIId*

The appropriate 5-aminopyrimidine[2] *III* (0.001 mol) was dissolved with stirring at 0°C in 1 ml of nitrosyl sulfuric acid previously prepared from 70 mg (0.001 mol) of sodium nitrite. The solution was treated with ice (10 g) (liberation of an equivalent amount of nitrogen). The mixture was then neutralised with aqueous potasium carbonate and diluted with a mixture (30 ml) of 1:1 dichloromethane—ethanol. The inorganic salts were removed, the organic layer separated, dried with calcinated potassium carbonate, and the solvent evaporated. The residue was crystallised from ethanol and sublimed under diminished pressure at 200°C; compound *IVb* was previously purified by column chromatography on silica gel (10% water) in 1 : 15 methanol—dichloromethane. The yields if compounds *IVa*, *IVb*, and *IVc* were 40%, 35% and 37%, resp. The identification was effected by elemental analyses, melting point determinations, IR spectra and mass spectra .

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