A NOVEL SYNTHESIS OF PYRIMIDINES. II. CYCLIZATION OF N-CYANO-CYANOACETAMIDINES

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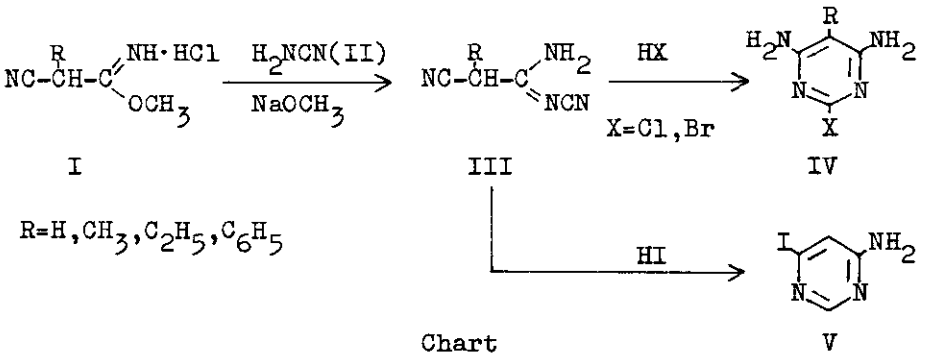
Cyclization reaction of N-cyano-cyanoacetamidines (III) with hydrogen chloride and bromide has been found to give 4,6-diamino-2-halogenopyrimidines(IV), but with hydrogen iodide to give an unexpected 4-amino-6-iodopyrimidine(V).

In our previous paper[1] we described the new synthesis of pyrimidines concerning the use of cyanoacetylcyanamides and their derivatives as intermediates. We wish to report an extension of these reactions to the synthesis of more useful pyrimidines by cyclization of N-cyano-cyanoacetamidines(III) with hydrogen halides (Chart). The amidines(III), which have a marked structural similarity to cyanoacetylcyanamides[1], were expected to undergo a similar cyclization reaction with hydrogen halides to pyrimidines. III were prepared according to F.C. Schaefer, et al.[2] by the reaction of cyanoacetimidates(I)[3] with cyanamide(II). General procedure was as follows.



Chart

A molar equivalent of methyl cyanoacetimidates(I) was added to a solution of II and sodium methoxide in methanol at 0-5° and then the reaction mixture was stirred for 2-3 h at room temperature. Sodium chloride was filtered off and the filtrate was evaporated to dryness. Crystallization of the residure from ethanol gave III (Table I).

The reaction of III with hydrogen halides(HCl,HBr) in acetic acid or acetone gave the salts of 4,6-diamino-2-halogeno-pyrimidines which were subsequently neutralized to free bases (IV) in fairly good yields (Table II), suggesting the cyclization reaction has proceeded in one specific direction. In marked contrast to hydrogen chloride and bromide, the treatment of IIIa with hydrogen iodide in acetic acid gave 4-amino-6-iodo-pyrimidine(V)[4] in a 43.5 % yield unexpectedly. General procedure for the preparation of IV was as follows. To a stirred suspension of III(0.01 M) in acetic acid(25 ml) was slowly introduced dry hydrogen halide gas or added dropwise a solution of hydrogen halide(0.04-0.06 M) in acetic acid at room temperature. After 4 hours, colorless precipitates were collected (or

the reaction mixture was evaporated to dryness) and neutralized with aq. Na_2CO_3 to yield IV. Recrystallization from appropriate solvent gave pure IV (Table II).

Table I N-Cyano-cyanoacetamidines(III)

compd.	R	yield(%)	mp(°C)
IIIa	H	76	126
IIIb	CH_3	48	141-142
IIIc	C_2H_5	47	97-99
IIId	C_6H_5	11	163.5-164.5

All compounds gave satisfactory analyses.

Table II 4,6-Diamino-2-halogenopyrimidines(IV)

compd.	R	X	yield(%)	mp(°C)	purification
IVa	H	Cl	51	273-274(d)	H_2O
IVb	CH_3	Cl	56	244-245	H_2O
IVc	C_2H_5	Cl	77	238.5-239.5	AcOEt-Acetone
IVd	C_6H_5	Cl	47	249-251	CH_3OH
IVe	H	Br	77	255(d)	CH_3OH
IVf	CH_3	Br	86	208-210	CH_3OH
IVg	C_2H_5	Br	95	241-244	CH_3OH
IVh	C_6H_5	Br	91	250-252	CH_3OH

Elemental analyses and spectral data were in accord with the compounds described.

The structures of III were identified by analyses, ir,nmr spectra and their cyclization to the pyrimidine rings upon treatment with hydrogen halides. The structures of IVa,e were confirmed by catalytic hydrogenation(Pd/C) to give 4,6-diaminopyrimidine[5] and the other pyrimidines(IVb-d,f-h) were characterized by analyses and by comparing of their spectral data(uv, ir,nmr) with those of IVa,e.

The method described in this paper for the preparation of 4,6-diamino-2-halogenopyrimidines, which have not been readily accessible or unavailable, provides many advantages over conventional method. Details of this investigation will be reported in the near future.

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