

A NOVEL SYNTHESIS OF PYRIMIDINES. I. CYCLIZATION OF
CYANOACETLYLCYANAMIDES AND THEIR DERIVATIVES

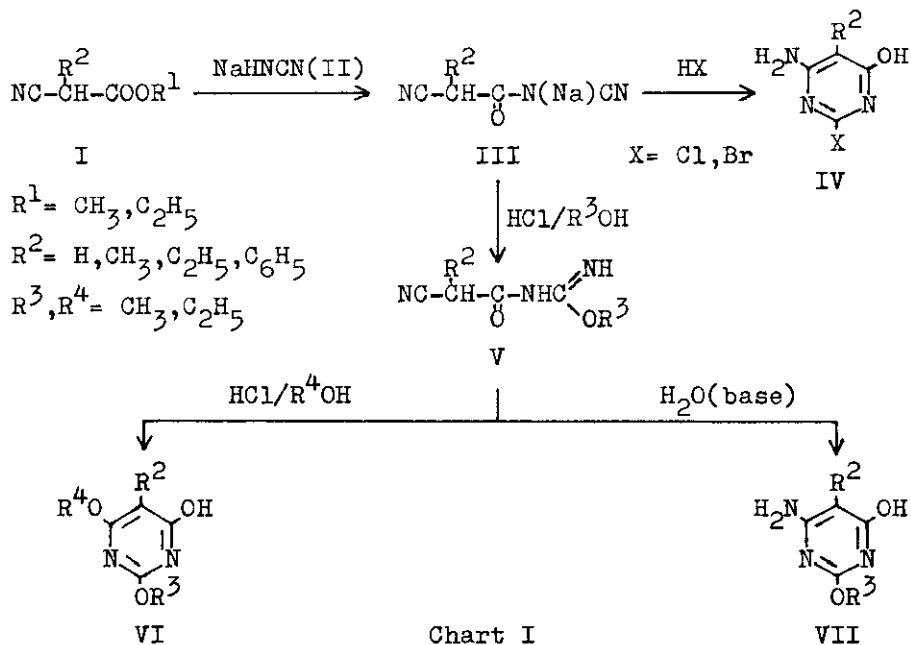
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Cyclization reaction of cyanoacetylcyanamides(III)
and their derivatives(V) has been found to give three
types of halogeno- and alkoxy-pyrimidines(IV,VI,VII).

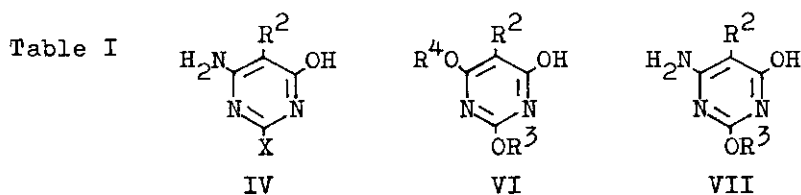
The cyclization reaction of α,ω -dinitriles with hydrogen
halides to various aromatic heterocyclic compounds were reported
by F.Johnson, et al.¹⁾, but no attempt has been made on the cycli-
zation of dinitriles to pyrimidine ring. We have found new
three routes(a,b,c) of pyrimidine synthesis by cyclization of
cyanoacetylcyanamides(III) and their derivatives(V) as shown in
Chart I. The starting materials, sodium salts of cyanoacetyl-
cyanamide(IIIa-d), were prepared according to J.H.Dewar, et al.²⁾,
by reaction of alkyl cyanoacetates(I) with sodium cyanamide(II)
in anhydrous methanol for 3-5 h at room temperature. [R²,
mp(°C), yield(%) : H, 197-198(d), 97 ; CH₃, 161-162, 98 ; C₂H₅,
87-91(1/2 hydrate), 90 ; C₆H₅, ca.50(monohydrate), 22].



The three cyclization reactions of pyrimidine synthesis were as follows.

a) The reactions of III with 4 to 6 M eq. of hydrogen halides in acetic acid or acetone for several hours at room temperature, followed by treatment of water and neutralization, gave 6-amino-2-halogeno-4-hydroxypyrimidines(IV) in good yields (Table I).

b) The reactions of III with alcoholic hydrogen chloride(10 M eq.) at room temperature afforded 2,6-dialkoxy-4-hydroxypyrimidines(VI) which were formed via N-cyanoacetyl-O-alkylisoureas(V). Therefore, in order to prepare VI having different alkoxy groups at the 2 and 6 positions of the pyrimidines, the intermediates (V) were isolated and then reacted with hydrogen chloride in the other alcohol (Table I). V could be obtained in good yields by



compd.	R ²	R ³	R ⁴	X	mp(°C)	yield(%)
IVa	H	-	-	Cl	>300	56
IVb	CH ₃	-	-	Cl	220	97
IVc	C ₆ H ₅	-	-	Cl	260-261(d)	72
IVd	H	-	-	Br	>280	72
VIa	H	CH ₃	CH ₃	-	195	26
VIb	CH ₃	CH ₃	CH ₃	-	224-226	47
VIc	C ₂ H ₅	CH ₃	CH ₃	-	221	12
VI d	C ₆ H ₅	CH ₃	CH ₃	-	239-240	60
VIe	H	C ₂ H ₅	CH ₃	-	150-152	27
VI f	H	CH ₃	C ₂ H ₅	-	184-185	32
VIIa ³⁾	H	CH ₃	-	-	221(d)	76
VIIb ⁴⁾	CH ₃	CH ₃	-	-	243	91
VIIc	C ₂ H ₅	CH ₃	-	-	226	49
VII d	C ₆ H ₅	CH ₃	-	-	241(d)	74
VIIe ⁵⁾	H	C ₂ H ₅	-	-	245-246(d)	75

Satisfactory analytical data were obtained for all new compounds.

reaction of III with alcoholic hydrogen chloride at 0-5°C, followed by neutralization with aq. NaHCO₃ solution (Table II).

c) Refluxing V in water in the presence of a weak base such as Na₂CO₃ afforded 2-alkoxy-6-amino-4-hydroxypyrimidines(VII) in good yields (Table I).

Table II N-Cyanoacetyl-O-alkylisoureas(V)

compd.	R ²	R ³	yield(%)	mp(°C)	purification
Va	H	CH ₃	75	118-119	H ₂ O
Vb	CH ₃	CH ₃	92	184-185*	HCl-CH ₃ OH
Vc	C ₂ H ₅	CH ₃	69	oil**	-
Vd	C ₆ H ₅	CH ₃	82	68-69	H ₂ O-CH ₃ OH
Ve	H	C ₂ H ₅	82	94-95	H ₂ O

* HCl salt ** characterized by spectral data

The structure assignments of III and V rest on elemental analysis, spectral data, and chemical behavior observed for their cyclization to the corresponding pyrimidines. The structures of the pyrimidines(IVa-d,VIa,VIIa,b,e) were confirmed by following methods(i-iv) and the other pyrimidines were characterized by comparison of their spectral data (uv,ir,nmr) with those of the confirmed pyrimidines.

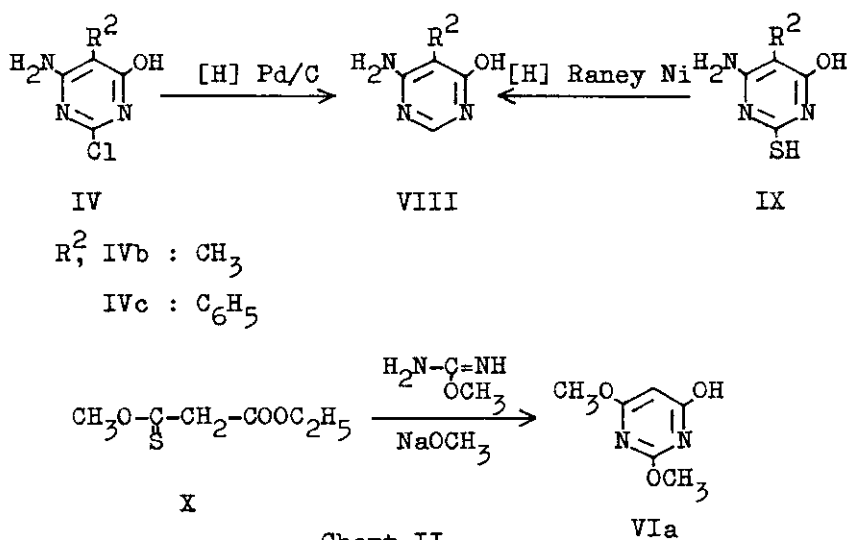
i) Structural assignments of VIIa,b,e were made on by direct comparison with authentic samples.^{3,4,5)}

ii) The structures of IVa,d were confirmed by methoxylation to VIIa.³⁾

iii) The structures of IVb,c were identified by hydrogenation

over Pd/C to 5-substituted 6-amino-4-hydroxypyrimidines(VIII; $R^2 = \text{CH}_3$, mp 240-242°C, $R^2 = \text{C}_6\text{H}_5$, mp 286-288°C(d)), which were prepared by hydrogenation(Raney nickel) from corresponding 5-substituted 6-amino-4-hydroxy-2-mercaptopyrimidines(IX)⁶⁾(Chart II).

iv) The structure of VIa was established by its independent synthesis from methyl ethoxycarbonylthioneacetate(X), bp 64-65°C (3 mm), with methylisourea (Chart II). X was prepared by an analogous procedure given by Barnikow and Strickmann.⁷⁾



Some of these pyrimidines(IV,VI) are relatively inaccessible by other methods.

Although numerous methods for the synthesis of pyrimidine rings were investigated by D.J.Brown,⁸⁾ our new methods provide

useful and convenient syntheses for preparing halogeno- and alkoxy-pyrimidines.

Details of this investigation will be reported in the near future.

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