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A NOVEL SYNTHESIS OF PYRIMIDINES. I. CYCLIZATION OF CYANOACETYLCYANAMIDES 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 cyclization 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 cyanoacetylcyanamide(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.[R^2, mp(°C), yield(%) : H, 197-198(d), 97 ; CH_3, 161-162, 98 ; C_2H_5, 87-91(1/2 hydrate), 90 ; C_6H_5, ca.50(monohydrate), 22].

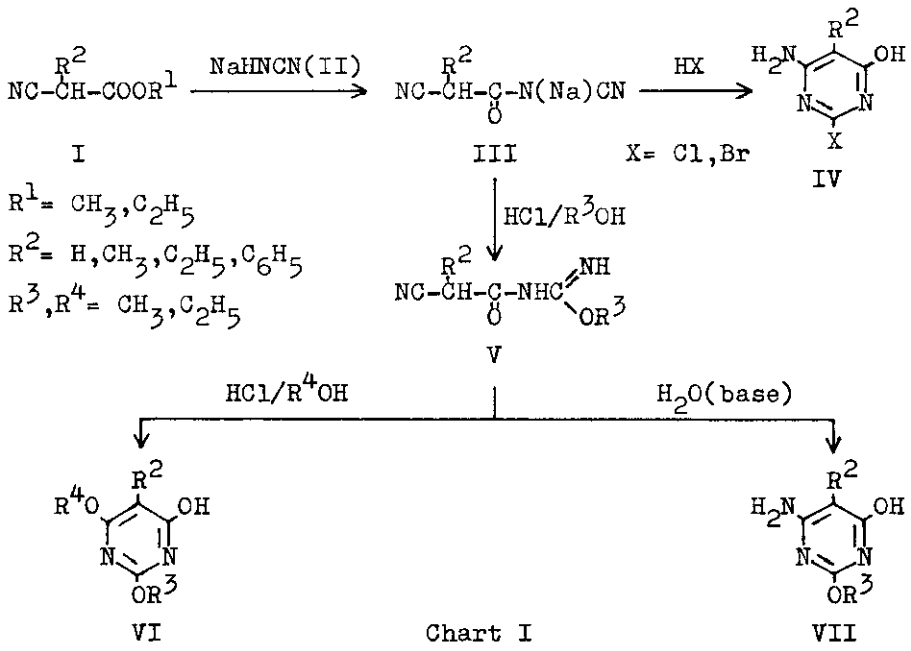


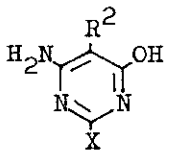
Chart I

The three cyclization reactions of pyrimidine synthesis were as follows.

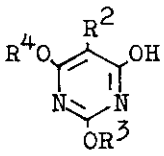
a) The reactions of III with 4 to 6 M eq. of hydrogen halides in acetic acid or acetone for several hours at room temperature, followed by treatment of water and neutralization, gave 6-amino-2-halogeno-4-hydroxypyrimidines(IV) in good yields (Table I).

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

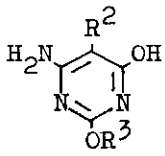
Table I



IV



VI



VII

compd.	R^2	R^3	R^4	X	mp(°C)	yield(%)
IVa	H	-	-	Cl	>300	56
IVb	CH_3	-	-	Cl	220	97
IVc	C_6H_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_2H_5	CH_3	CH_3	-	221	12
VId	C_6H_5	CH_3	CH_3	-	239-240	60
VIe	H	C_2H_5	CH_3	-	150-152	27
VIf	H	CH_3	C_2H_5	-	184-185	32
VIIa[3]	H	CH_3	-	-	221(d)	76
VIIb[4]	CH_3	CH_3	-	-	243	91
VIIc	C_2H_5	CH_3	-	-	226	49
VIId	C_6H_5	CH_3	-	-	241(d)	74
VIIe[5]	H	C_2H_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. $NaHCO_3$ solution (Table II).

c) Refluxing V in water in the presence of a weak base such as Na_2CO_3 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_2O
Vb	CH_3	CH_3	92	184-185*	HCl-CH_3OH
Vc	C_2H_5	CH_3	69	oil**	-
Vd	C_6H_5	CH_3	82	68-69	H_2O-CH_3OH
Ve	H	C_2H_5	82	94-95	H_2O

* 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.

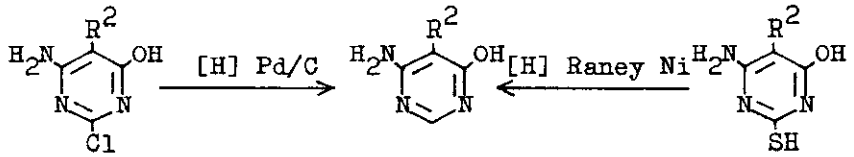
i) Structural assignments of VIIa,b,e were made on by direct comparison with authentic samples.[3,4,5]

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= CH_3, mp 240-242°C, R^2= C_6H_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).

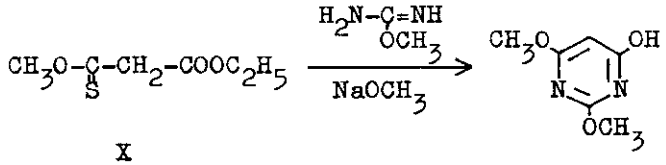
iv) The structure of VIa was established by its independent synthesis from methyl ethoxycarbonylthioneacetate(X),bp 64-65°C (3 mm), with methylisourea (Chart II). X was prepared by an analogous procedure given by Barnikow and Strickmann.[7]



IV VIII IX

R^2; IVb : CH_3

IVc : C_6H_5



X VIa

Chart II

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.

ACKNOWLEDGEMENT

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REFERENCES

1) a) F.Johnson, 'Advances in Heterocyclic Chemistry', eds. by A.R.Katrizky, Acad.Press, New York & London, 1966, 6, p.128.
b) W.A.Nasutavicus and F.Johnson, J.Org.Chem., 1968, 32, 2367.
c) W.A.Nasutavicus, R.W.Tobey, and F.Johnson, ibid., 1968, 32, 3325.
2) J.H.Dewar and G.Shaw, J.Chem.Soc., 1965, 1642.
3) Dan.Pat., 1970, 116,591. Chem.Abstr., 1970, 73, 109792^{t}.
4) W.Pfleiderer and G.Strauss, Annalen., 1958, 612, 173.
5) Frdl., 1902-4, 7, 683.
6) Ger.Pat., 1952, 859,168. Chem.Abstr., 1956, 50, 9452^{h}.
7) G.Barnikow and G.Strickmann, Chem.Ber., 1967, 100, 1428.
8) D.J.Brown, 'The Pyrimidines', John Wiley & Sons Inc., New York & London, 1962, p.31-110.

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