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A NEW SYNTHESIS OF 6-CHLORO-2-METHYL- AND 6-CHLORO-2-ETHYL-5-METHYL-4(3H)-PYRIMIDONES

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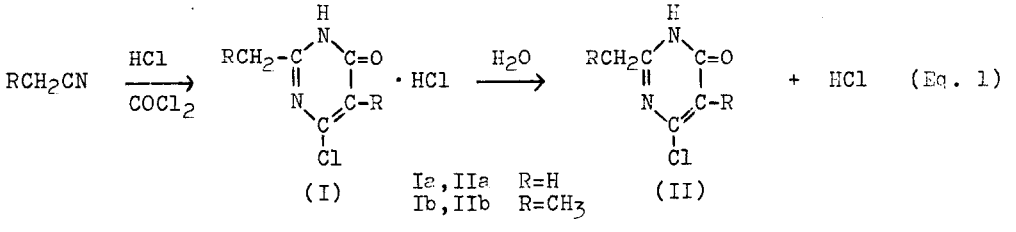
The reaction between nitriles and phosgene was reported by Henke (1) in 1858, but it has been considered that the phenomenon was probably one of mere solution. (2)

We have found that when acetonitrile containing hydrogen chloride is allowed to react with phosgene in a sealed glass tube at 60-65° for 40 hours (mole ratio of hydrogen chloride to phosgene is 0.9), 6-chloro-2-methyl-4(3H)-pyrimidone hydrochloride (Ia) is obtained in 55.4% yield; mp above 240° (dec.) and ν max 1730 cm^{-1}, 1640 cm^{-1} (C=O and/or ring (3))(KBr disc). Anal. Found: C, 33.49; H, 3.24; N, 15.69; Cl, 38.8. Calcd. for $C_5H_6Cl_2N_2O$: C, 33.18; H, 3.34; N, 15.48; Cl, 39.17. Washing Ia with water (Eq. 1) gives 6-chloro-2-methyl-4(3H)-pyrimidone (IIa) almost quantitatively; mp 235.5-236.5° [lit (4) 231.5-232.0°], ν max 1685 cm^{-1}, 1600 cm^{-1} (C=O and/or ring)(KBr disc). Anal. Found: C, 41.33; H, 3.22; N, 19.54; Cl, 24.3. mol wt 143. Calcd. for $C_5H_5ClN_2O$: C, 41.54; H, 3.49; N, 19.38; Cl, 24.52. mol wt 144.6.

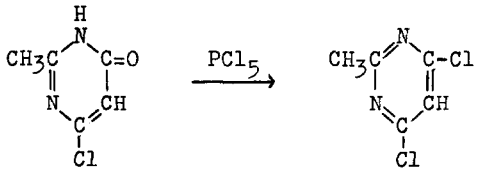


(I) Ia, IIa R=H; Ib, IIb R=CH_3 (II)

(Eq. 1)

The nmr spectrum of IIa, measured in pyridine, exhibited a singlet at τ 7.60 (3H)(assigned to methyl protons) and a singlet at τ 3.48 (1H)(assigned to the ring proton).

Further, the pyrimidone (IIa) was identified by converting it to 4,6-dichloro-2-methyl-pyrimidine (III) by reaction with phosphorus pentachloride (Eq. 2); mp 45.0-45.5° [lit (3) 46-48°]; ν max 1530 cm^{-1} (ring). Anal. Found: Cl, 43.7. mol wt 166. Calcd. for $C_5H_4Cl_2N_2$: Cl, 43.50. mol wt 163.0 nmr ($CDCl_3$): τ 7.29 (singlet 3H), τ 2.74 (singlet 1H)



(IIa) (III) (Eq. 2)

The melting point, I.R. and nmr spectra of compound III were identical with those of an authentic sample prepared by the reaction of 2-methyl-4,6(1H, 5H)-pyrimidinedione with phosphorous oxychloride; mixture melting point showed no depression.

The pyrimidone (IIa) reacts with dry hydrogen chloride to give compound Ia and IIa can be regenerated by treating Ia with water or by recrystallization from water or methyl alcohol. Sublimation of Ia under reduced pressure also yields IIa. These facts indicate that the pyrimidone (Ia) is a weak base but can form an unstable salt with hydrogen chloride.

Recently, Nishiwaki (5) reported that in nmr spectrum, NH-signal of 4-pyrimidones could be seen as a broad peak in low field and pronounced concentration dependence was noted. However, the signal corresponding to NH proton of IIa was not observed.

Similarly, propionitrile furnishes 6-chloro-2-etyl-5-methyl-4(3H)-pyrimidone (IIb) through Ib in 38.9% yield; mp 203-204.5°; ν max 1670 cm^{-1}, 1600 cm^{-1} (C=O and/ro ring)(KBr disc), Anal. Found: C, 48.44; H, 5.22; N, 16.31; Cl, 20.56. mol wt 172. Calcd. for $C_7H_9ClN_2O$: C, 48.71; H, 5.26; N, 16.23; Cl, 20.54. mol wt 172.6.

The nmr spectrum of IIb measured in $CDCl_3$, exhibited a triplet at τ 8.65

(3H, J=7.5 cps, assigned to methyl protons of ethyl group), a singlet at τ 7.85 (3H, assigned to 5-methyl protons) and a quartet at τ 7.26 (2H, J=7.5 cps, assigned to methylene protons). No NH.proton was observed in the region between τ -5.8 and 10.

Although there are various methods for elaborating the pyrimidine nucleus (6), the present method provides a new and convenient synthesis of 6-chloro-2,5-dialkyl-4(3H)-pyrimidone.

Further work to clarify the scope, limitation and mechanism of this new chloropyrimidones synthesis is under progress.

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