# Ready Ring-opening of Some Pyrimidine Derivatives

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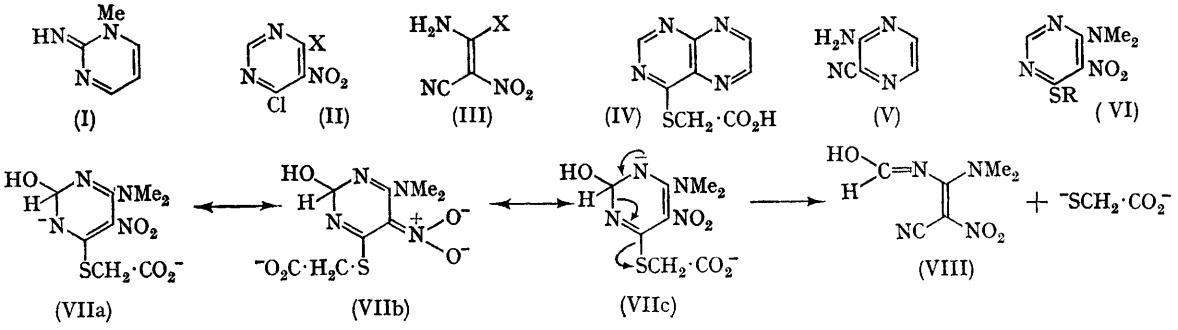
PYRIMIDINE derivatives are normally fairly resistant to ring-opening by acids and bases.[1] Pyrimidine itself is decomposed by heating with 30% sodium hydroxide solution[2] but the introduction of electron-donating groups, such as hydroxy-, amino-, or thio-, tends to increase the stability. Conversely, electron-withdrawing groups tend to reduce stability, so that 5-nitropyrimidine is readily decomposed by alkali although it is fairly stable to acid.[3] Nuclear-*N*-alkylated iminopyrimidines [*e.g.*, (I)] undergo the Dimroth rearrangement which involves ring-opening.[4]

It is now shown that certain compounds (II) undergo ring cleavage, with great ease, to yield nitriles (III) by a mechanism not previously observed in the pyrimidine series. For example, (II; X = $NMe_2$) yielded (III; X = $NMe_2$) (50—60%) on heating with dilute acetic, chloracetic, trifluoroacetic, or hydrochloric acid. Another tertiary amine (II; X = morpholino) gave a high yield (94%) of the corresponding nitrile (III; X = morpholino), but the secondary amine (II; X = NHMe) gave only 18% of the nitrile (III; X = NHMe), and the primary amine (II; X = $NH_2$) gave none of the possible product (III; X = $NH_2$).




The reaction appears to involve attack, by a nucleophilic species (*e.g.*, a water molecule, hydroxide ion, or acetate ion) at the unsubstituted 2-position of the pyrimidine, or one of its several possible cations, and subsequent loss of a chloride ion. Uncertainty in the position of protonation of the pyrimidine (II) makes it difficult to give a precise mechanism for reactions in acid conditions. However cleavage of some fused pyrimidine derivatives, typified by 4-carboxymethylthiopteridine (IV), has been reported to occur in alkaline conditions to give *o*-amino-nitriles (*e.g.*, V)[5]. The close similarity between those reactions and the present ones suggested that the pyrimidine (VI; R = $CH_2 \cdot CO_2H$ (might cleave in alkaline conditions. In fact cleavage occurred so readily that treatment of the mercapto-compound (VI; R = H) with chloroacetic acid in sodium carbonate yielded the nitrile (III; X = $NMe_2$) directly. It seems clear that attack by hydroxide ion, gives a resonance-stabilised intermediate (VII), which loses $-SCH_2 \cdot CO_2^-$ (VIIc), to yield the penultimate product (VIII). Previously, a second substituted ring has always been present when this type of mechanism has been operative,[5] but it appears that the nitro-group is equally effective in stabilising the intermediate (VII) and in activating the 2-position to nucleophilic attack. Bulky, substituted, amino-groups are most effective in position 4(6) and a good leaving group ($Cl^-$; $-SCH_2 \cdot CO_2^-$) is necessary in position 6(4). It seems likely that the reactions in acid media involved attack by a weak nucleophile (*e.g.*, $H_2O$) on a pyrimidine cation while the reaction in alkaline medium involved a powerful nucleophile ($OH^-$) and a pyrimidine anion (VI; R = $CH_2 \cdot CO_2^-$).

Satisfactory elemental analyses have been obtained for all the compounds mentioned. The following data apply to the nitrile (III; X = $NMe_2$); m.p. 186—187°; infrared: ν(NH) 3360, 3230, ν(CN) 2210; ν(C=C) 1665 $cm.^{-1}$; $^1H$ n.m.r.: singlet τ 6·96 (6H), singlet τ 1·6 (2H, removed on deuteration).

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