CONVERSION OF 4-CHLORO-5-NITROPYRIMIDINES TO 1,3,5-TRIAZINES USING ALKYLISOTHIOUREAS

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Treatment of 2-amino-4-chloro-6-methyl- and 2-methylthio-4,6-dichloro-5-nitropyrimidines with alkylisothioureas in the presence of base (aqueous NaOH solution) gives the corresponding alkylthiopyrimidines [1, 2].

We have attempted to extend this reaction to other 4-chloro-5-nitropyrimidines. Dependent upon the nature of the substituents the reaction may not stop at exchange of the chlorine atoms for a thioalkyl group but the 4-chloro-5-nitropyrimidines may be converted to a 1,3,5-triazine as a result of a number of consecutive reactions.

Hence treatment of 4,6-dichloro-5-nitro- and 2-methyl-4,6-dichloro-5-nitropyrimidines (Ia, b) with S-methylisothiourea (IIa) in aqueous alkali gave the 1,3,5-triazines 3,4-dihydro-2-methylthio-4-(1-cyano-1-nitromethylene)-1,3,5-triazine (IIIa) and its 6-methyl analog IIIb in yields exceeding 70%. The yield of 4,6-bismethylthio-5-nitropyrimidine (IVa) and its 2-methyl homolog IVb were obtained in 6 and 15% yields, respectively. Similarly 4-methoxy-5-nitro-6-chloropyrimidine (Ic) gave the sym-triazine IIIa (62% yield) and 6-methylthio-4-methoxy-5-nitropyrimidine IVc (20%). Treatment of Ia with S-benzylisothiourea (IIb) gave 2-benzylthio-3,4-dihydro-4-(1-cyano-1-nitromethylene)-1,3,5-triazine IIIc (55%) and 4,6-bisbenzylthio-5-nitropyrimidine IVd (11%).

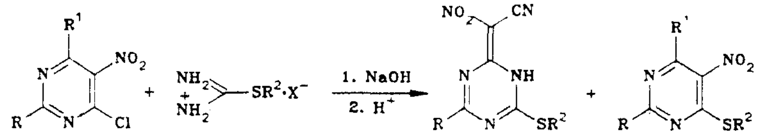
In contrast, the reaction of 4-dimethylamino-5-nitro-6-chloropyrimidine (Id) with urea IIa gave 80% of 4-dimethylamino-6-methylthio-5-nitropyrimidine IVe. In this case formation of a 1,3,5-triazine did not occur.

The mixtures of sym-triazines III and alkylthiopyrimidines IV were separated by refluxing in benzene. The insoluble residue was treated with HCl to give III. Compound IV was separated from the benzene extract (see Table 1).

The structures of IIIa-c were confirmed by ^1H and ^{13}C NMR spectroscopy. Thus the PMR spectra of these compounds in DMSO-D_6 show signals for the thioalkyl group (SR^2), the aromatic proton at ≈8.6 ppm or the methyl at ≈2.5 ppm, and the absence of a methylene proton signal. The ^{13}C NMR spectrum of IIIa (DMSO-D_6 showed a signal as a broadened singlet at 129.7 ppm (spin—spin interaction with the ring NH group) corresponding to the methylene fragment carbon atom.

Compounds IIIa-c and IVa-e are yellow crystalline materials, stable on storage. Compounds IIIa-c are readily soluble in aqueous base.

TABLE 1. Compounds Studied



Ia-d IIa,b IIIa-c IVa-e

Compound	R	R¹	Compound	R	R²	X⁻	Compound	R	R¹	R²
Ia	H	Cl	IIa		Me	HSO_4^-	IVa	H	SMe	Me
Ib	Me	Cl	IIb		CH_2Ph	Cl^-	IVb	Me	SMe	Me
Ic	H	OMe	IIIa	H	Me		IVc	H	OMe	Me
Id	H	NMe_2	IIIb	Me	Me		IVd	H	SCH_2Ph	CH_2Ph
			IIIc	H	CH_2Ph		IVe	H	NMe_2	Me

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Compound IIIa. Mp 160-162°C (from ethanol) **IIIb:** mp 185-186°C (acetone); **IIIc:** mp 167-169°C (ethanol); **IVa**: mp 142-143°C (benzene—hexane); **IVb:** mp 181-183°C (benzene—hexane); **IVc:** mp 138-140°C (benzene—hexane); **IVd:** mp 92-94°C (hexane); **IVe:** mp 70-72°C (ethanol).

Elemental analytical data for III and IV agreed with that calculated.

This reaction of 5-nitropyrimidines to 1,3,5-triazines adds to the literature data concerning the transformation of the pyrimidine to the 1,3,5-triazine ring system. Similar reactions have been reported, for example, with 5-nitroso- and 2-amino-4-chloropyrimidines [3, 4].

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