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STUDIES ON PYRIMIDINE DERIVATIVES. IV[1] SYNTHESIS OF HYDROXYMETHYLPYRIMIDINES BY MEANS OF THE HOMOLYTIC HYDROXYMETHYLATION

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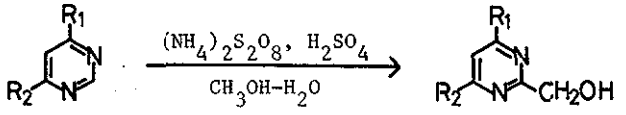
2-Hydroxymethyl- and 4-hydroxymethyl-pyrimidines were synthesized in yield ranging from 28 to 93% by the reactions of some simple pyrimidine derivatives with the hydroxymethyl radical generated from methanol and ammonium peroxydisulfate.

There are not a great many pyrimidines with a hydroxymethyl group directly to the 2- or 4-position of the ring. The Cannizzaro reaction of pyrimidine aldehydes or the LAH reduction[2] of pyrimidine carboxylic esters have been sometimes used for the synthesis of hydroxymethylpyrimidines. However, since preparations of pyrimidines containing a formyl or an ethoxycarbonyl group by the ring closure reaction are limited, these methods

are not of wide application.

Recently Minisci et al.[3] have reported that treatment of N-heteroaromatics such as pyridine and benzopyridine with ammonium peroxydisulfate and methanol is a promising and convenient method for introduction of a hydroxymethyl group into the α- and γ-positions of these nuclei. This reaction involves an attack of $\cdot CH_2OH$ radical, and the presence of an electron-withdrawing group on heteroaromatic nuclei promotes the reaction.

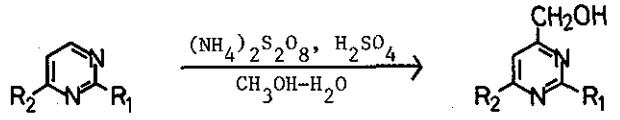
We now wish to report the application of this hydroxymethylation to some simple pyrimidines leading to the 2- and 4-hydroxymethylpyrimidines in yield ranging from 28 to 93%. A typical experiment is as follows. 4,6-Dimethylpyrimidine (Ia), (50 mmole), ammonium peroxydisulfate (100 mmole) and water (45 ml) were dissolved in methanol (90 ml) with an equivalent mole (3.5 ml) of sulfuric acid. After heating the solution at 80° for 24 hr, a half volume of the solvent was removed under reduced pressure, and the residue was carefully made alkaline with potassium carbonate and extracted with chloroform. The chloroform extract was concentrated to give 2-hydroxymethyl-4,6-dimethylpyrimidine (IIa), mp 87-88°,[4] in 93% yield. Elemental analysis ($C_7H_{10}ON_2$) and the spectral data of IIa [IR ($CHCl_3$) cm^{-1} 3450 (OH); NMR δ ($CDCl_3$) 2.50 (6H, s, $-CH_3$), 4.75 (2H, s, $-CH_2OH$), 6.95 (1H, s, -CH=), 4.05 (1H, s, OH)] were in good agreement with the assigned structure. The hydroxymethylation of 4-methyl-6-phenyl- (Ib) and 4-methoxy-6-methyl-pyrimidine (Ic) afforded the corresponding 2-hydroxymethyl derivatives (Table I).



Ia,b,c IIa,b,c

Compd. No.	Substituents		mp or bp (°C)	Yields (%)	IR $\nu_{max}^{CHCl_3}$ (cm^{-1})(OH)	NMR($CDCl_3$) δ (ppm)	
	R_1	R_2				$-CH_2OH$	$-OH$
IIa	CH_3	CH_3	87-88	93	3450	4.75(2H,s)	4.05(1H,s)
IIb	CH_3	C_6H_5	149-150 (1mmHg)	48	3470	4.64(2H,s)	3.52(1H,s)
IIc	CH_3	OCH_3	56.5-57	42	3450	4.62(2H,s)	3.65(1H,s)

Table I



IIIa,b,c,d IVa,b,c,d

Compd. No.	Substituents		mp or bp (°C)	Yields (%)	IR $\nu_{max}^{CHCl_3}$ (cm^{-1})(OH)	NMR($CDCl_3$) δ (ppm)	
	R_1	R_2				$-CH_2OH$	$-OH$
IVa	CH_3	C_6H_5	95-96	65	3420	4.75(2H,s)	3.90(1H,s)
IVb	C_6H_5	CH_3	151-152 (1mmHg)	64	3400	4.68(2H,s)	3.4-4.2 (1H,broad)
IVc	CH_3	OCH_3	116-116.5	42.5	3400	4.60(2H,s)	3.85(1H,s)
IVd	OCH_3	CH_3	146-147	28	3400	4.62(2H,s)	3.6-4.2 (1H,broad)

Table II

Subsequently, the reaction of 2,6-disubstituted pyrimidines (IIIa,b,c,d) were similarly carried out and the respective 4-hydroxymethyl derivatives (IVa,b,c,d) were obtained (Table II). However 4-hydroxymethyl derivative could not be isolated from the reaction of 2,6-dimethylpyrimidine.

Observing the data in Table I and II, it was concluded that the pyrimidine derivatives (I,III) were superior in reactivity to pyridine derivatives and that the presence of a methoxyl group lowered the yield. This hydroxymethylation provides a facile route to the useful pyrimidine methanols which have not been synthesized by other manner. The oxidation of II and IV to pyrimidine aldehydes are now under investigation in our laboratory.

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