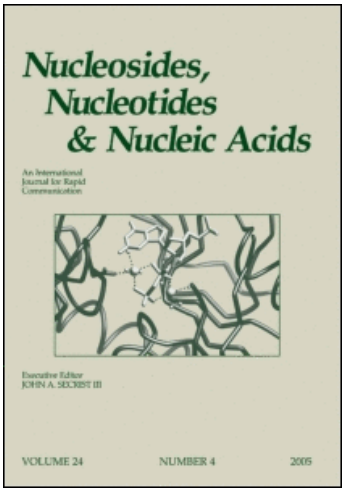

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THE INTRODUCTION OF C-SUBSTITUTENTS INTO PYRIMIDINE- AND PURINE-NUCLEOSIDES

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Abstract

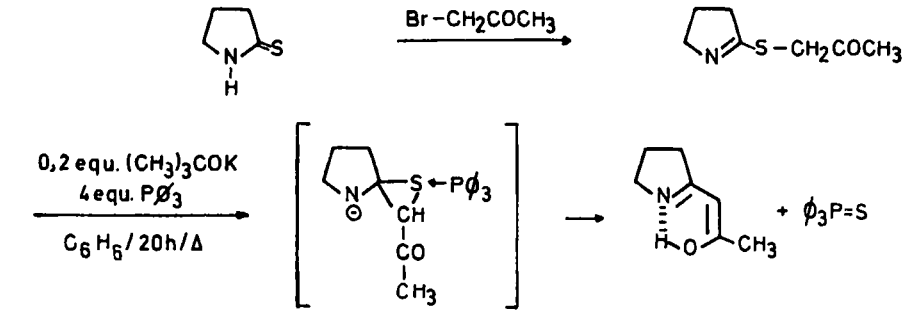
The introduction of C-substituents into pyrimidine and- purine-nucleosides by sulfide contraction [compare Ang. Chem. 88, 724 (1976), Int. Ed. 15, 689 (1976)] will be discussed with the emphasis on unpublished work.

For more than 15 years, we have been interested in the introduction of C-substituents into nucleosides and N-heterocycles in general. A lecture by Professor Eschenmoser on his sulfide-contraction stimulated our interest in this reaction. [1] We synthesized then (1971 - 1972) 6-phenacylnebularine from 6-mercaptonebularine, but only got around to finish some more work when I was invited to give a lecture at the first Gordon Conference on purines in 1976 organized by the late G. B. Brown. The results of this work were published in the same year as a preliminary publication in Angew. Chem. [2]. This was fortunate because in 1977 a preliminary publication [3] and in 1980 a full publication [4] appeared by T. Ueda and his coworkers, who had independently applied the sulfide contraction to nucleosides and had obtained very similar results with 6-mercaptopurine- and 4-thio-pyrimidine-nucleosides.

Today, I want to give a brief progress report on some completed and some ongoing work with this reaction.

S-alkylated thiolactam systems containing an acidic C-H group give with bases episulfide-intermediates which are desulfurized by trivalent phosphorous compounds with formation of a new C-C bond. (Scheme 1)

Sulfide Contraction (Sulfur-Extrusion)



A. Eschenmoser+al, Helv. Chim. Acta 54, 710 (1971)

Scheme 1

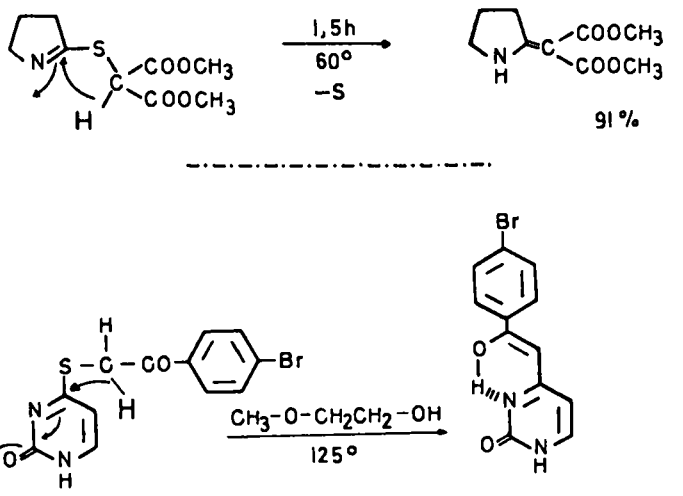
This type of reaction is especially facile when the sulfide-anion is stabilized by two acceptor groups or when the cyclic thioimino-ester-system contains an acceptor like a carbonyl group. In these cases sulfide contraction occurs even while heating in the absence of phosphines. [5] (Scheme 2)

After completed sulfide-contraction the newly formed compounds can be further modified e.g. by retro-aldol reactions, which occur on longer exposure or heating e.g. with sodium methylate in methanol. (Scheme 3)

Thus phenacyl-nucleosides are converted to the corresponding methyl or substituted methyl compounds and cyclic ketones are cleaved to the corresponding ω-alkoxycarbonyl-alkyl-nucleosides.

However, it should be pointed out here that other anion-stabilizing groups like nitrile-, nitro-, sulfo- or silyl groups, which will also facilitate sulfide contraction-reactions, can also be removed later by alternative methods e.g. reduction with Bu_3SnH, NaHg or fluoride treatment as exemplified for the case of 4-thiopyrimidine-nucleosides. (Scheme 4)

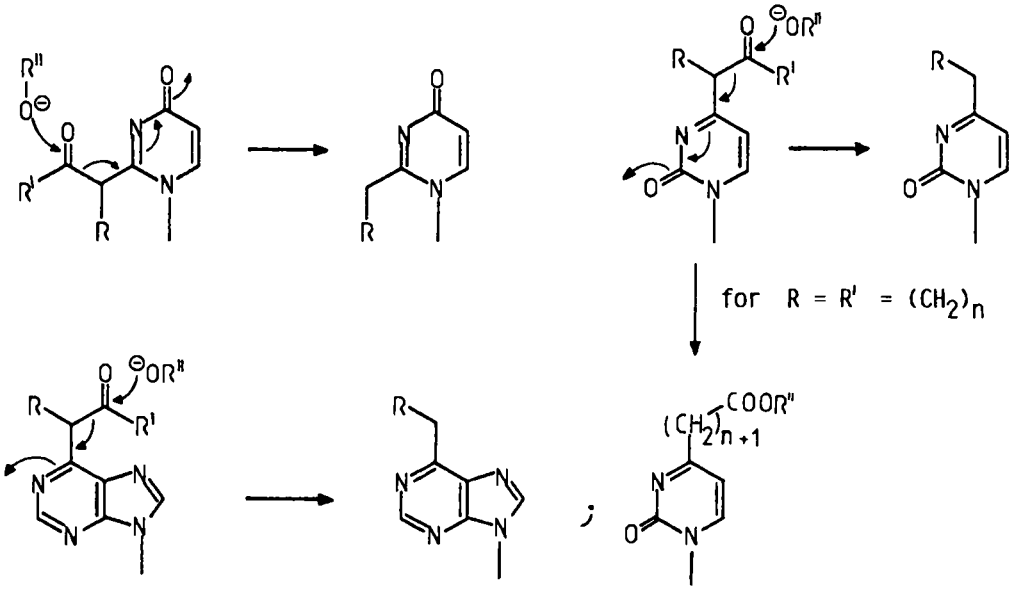
6-Mercapto-nebularine-tri-O-acetate is readily alkylated by phenacyl chloride to give 6-S-phenacyl-nebularine, which affords on



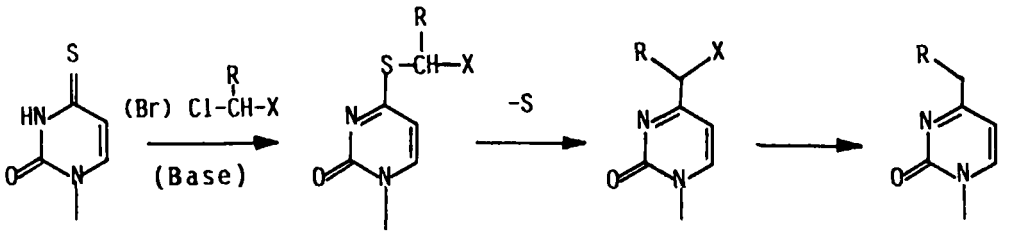
B. Roth (cited by A. Eschenmoser) JOC 45 3651 (1980)

Scheme 2

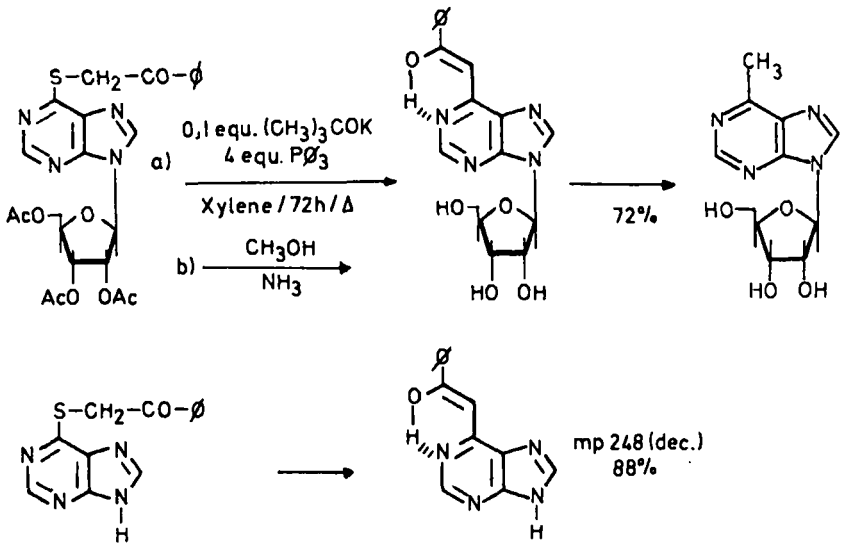
RETRO-ALDOL-REACTION



Scheme 3



Scheme 4

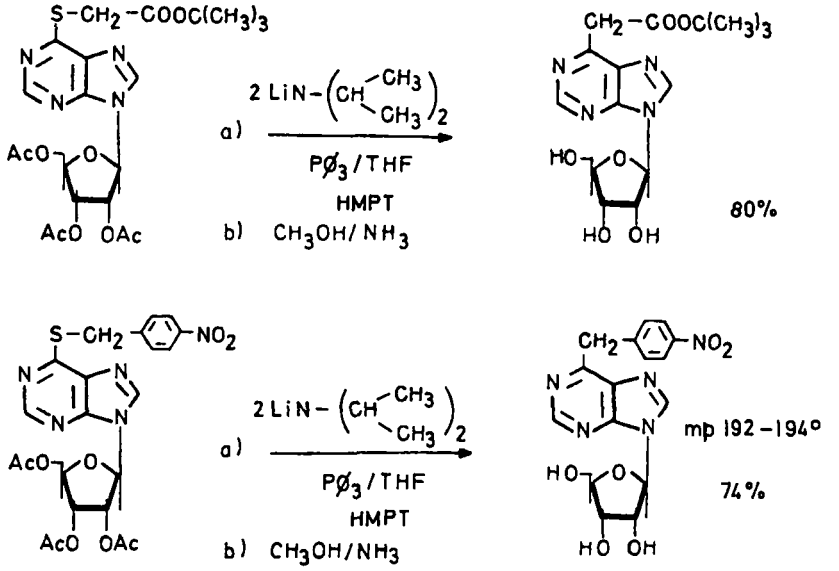


Scheme 5

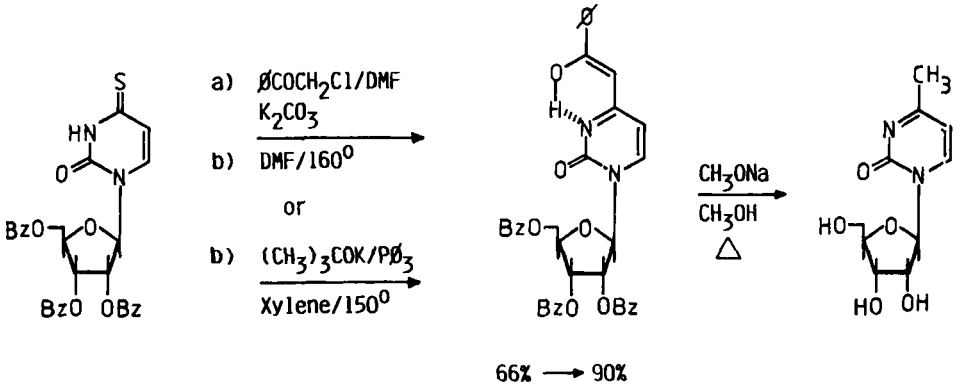
sulfide contraction 6-phenacyl-nebularine in high yield. Retro-aldol cleavage with sodium methylate gives 6-methyl-nebularine in high yield. (Scheme 5)

Analogously, the tert. butylester of 6-thio-nebularine acetic acid as well as the p-nitrobenzyl-thio compounds containing a vinylogous nitro group (compare scheme 6), furnished the corresponding substituted 6-methylnebularines.

S-alkylation of protected 4-thio-uridine with phenacyl chloride and subsequent heating in DMF or preferably treatment with potassium t-butylate and triphenylphosphin gives the protected 4-phenacyl com-



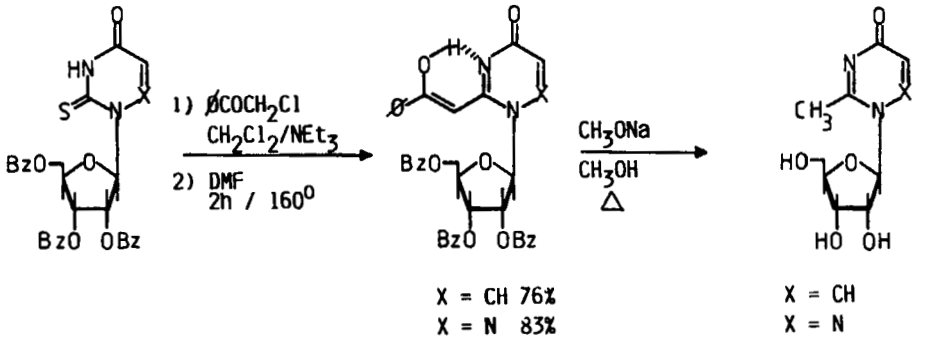
Scheme 6

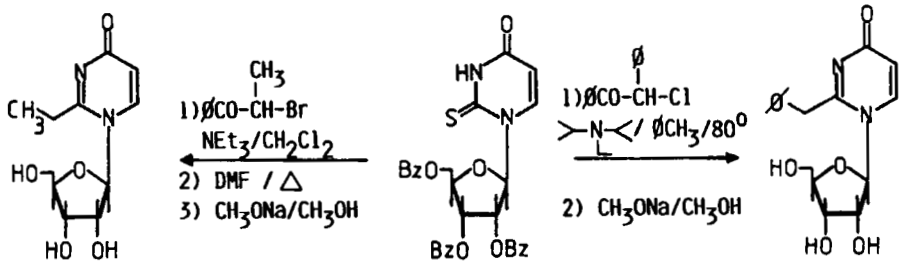


Scheme 7

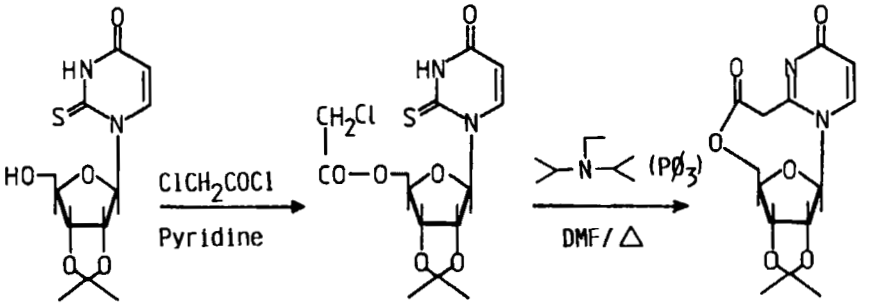
pound in high yields. Deprotection and simultanous retro-aldol reaction affords free 4-methyl-4-desoxy-uridine. (Scheme 7)

More interesting are the reactions of protected 2-thio-uridine and 2-thio-6-azauridine. Alkylation with phenacylchloride and subsequent deprotection/retro-aldol reaction furnished the corresponding 2-methyl-derivatives in high yields. (Scheme 8)





Scheme 8



Scheme 9

Alkylation with bromo-propiophenone or desylchloride followed by sulfide contraction and deprotection/retro-aldol reaction is being investigated to give the corresponding 2-ethyl- or 2-benzyl-derivatives, which are difficult to prepare by alternative routes. The ongoing experiments seem to indicate that the free 2-desoxy-2-benzyl-uridine is rather acid-labile.

Experiments are underway to cyclize the 2,3-isopropylidene-5-O-chloroacetyl-2-thiouridine followed by sulfide-contraction to the corresponding 9-membered lactone. (Scheme 9)

We hope that these experiments will convince you that the potential and the scope of the sulfide-contraction has not as yet been fully explored. We believe that the sulfide-contraction will be used as a powerful tool for the introduction of C-substituents into nucleosides giving products like 2-substituted pyrimidine nucleosides which are difficult to prepare by alternative methods.

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