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A CONVENIENT METHOD FOR THE SYNTHESIS OF 5'-S-ALKYLTHIO-5'-DEOXYRIBONUCLEOSIDES

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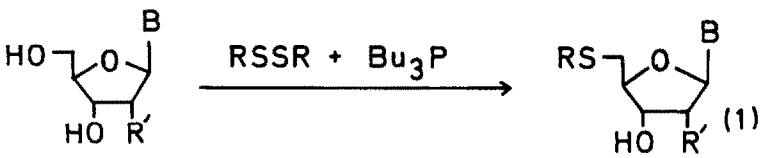
An interest in the physiological properties of sulfur containing nucleoside led us to study a new synthetic route for the synthesis of sulfur containing nucleosides. O-Tosyl nucleosides,[1] O-mesyl nucleosides,[2] halonucleosides,[3] and cyclonucleosides[4] were known as useful synthetic intermediates for the synthesis of sulfur containing nucleosides. Holý reported 5'-(pyrimidin-2-yl-thio)-5'-deoxyribonucleosides prepared from the reactions of nucleosides with 2-mercaptopyrimidine in the presence of dimethylformamide dialkylacetals.[5] Recently, we have found that a combined reagent of diphenyl disulfide and tri-n-butylphosphine is a useful one for introduction of phenylthio group to phosphate residue on nucleotides.[6]

In this communication we wish to report the selective synthesis of 5'-S-alkylthio-5'-deoxyribonucleosides (1) by the reactions of nucleosides with dialkyl disulfides and tri-n-butylphosphine.



B =nucleoside base, R'= H, OH

When uridine (0.5 mmole) was treated with diphenyl disulfide (1.5 mmole) in the presence of tri-n-butylphosphine (1.5 mmole) in dry pyridine (0.25 ml) at room temperature for 24 hr, 5'-S-phenylthio-5'-deoxyuridine was obtained in 83% yield. In this reaction, when 2,2'-dipyridyl disulfide was used in place of diphenyl disulfide, 5'-S-pyridylthio-5'-deoxyuridine was obtained in 78% yield.

In a similar manner, several 5'-S-pyridylthio derivatives of nucleosides were obtained in high yields. 5'-S-(N,N-diethyl)dithiocarbamoyl-5'-deoxyuridine was also obtained in 90% yield when N,N-diethylthiocarbamoyl disulfide was employed.

By this method, vitamin L_2, 5'-S-methylthio-5'-deoxyadenosine[3a] was synthesized in 73% yield by the reaction of adenosine (1 mmole) and dimethyl disulfide (10 mmole) in the presence of tri-n-butylphosphine (10 mmole) in dry dimethyformamide (5 ml) at room temperature for 24 hr.

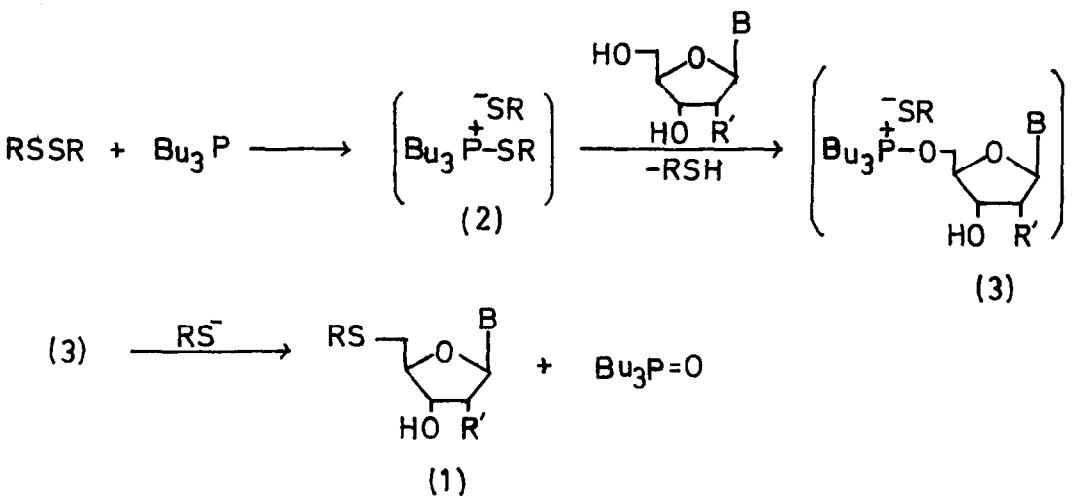
These results are summarized in Table 1.

Table 1. Synthesis of 5'-S-Alkylthio-5'-deoxyribonucleosides (1)

nucleoside	disulfide (RSSR) R	yield (%)	m.p. (°C)	spectral data (nm) λ_{max}^{MeOH}	λ_{min}^{MeOH}
uridine	2-pyridyl	78	168	251	226
cytidine	2-pyridyl	87	107-109	247, 277	224, 263
adenosine	2-pyridyl	quant.	84-93(dec.)	252	226
2'-deoxythymidine	2-pyridyl	26	180-181	250	231
2'-deoxycytidine	2-pyridyl	56	184-185	247, 277	224, 263
uridine	phenyl	83	206-207	256	229
uridine	$(C_2H_5)_2NC(S)$	90	155-156	254, 268	232, 262
2'-deoxythymidine	$(C_2H_5)_2NC(S)$	93	129-130	273	234
adenosine	methyl	73	207-208	260	228

In the above experiments, the reactions proceeded sluggishly when triphenylphosphine or triphenyl phosphite was used in place of tri-n-butylphosphine.[7)]

From the facts, the reaction seems to proceed through a phosphonium salt (2) which in turn reacts with nucleoside to form the nucleoside 5'-O-phosphonium salt (3).[8)] This phosphonium salt (3) further reacts with thiolate ion to give the corresponding 5'-S-alkylthio-5'-deoxyribonucleoside (1).



In conclusion, it is noted that this method has three advantageous points, namely: (1) no side-reaction, such as the formation of cyclonucleoside, was observed; (2) the reaction proceeds smoothly at room temperature under neutral condition; (3) the alkylthio groups can be introduced selectively to 5'-position on sugar moiety of nucleoside even when an excess amount of dialkyl disulfide was used.

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8) Mitsunobu and his-coworkers proposed the same type of intermediate for the regiospecific acylation and amination of nucleosides by means of diethyl azodicarboxylate and triphenylphosphine: (a)O.Mitsunobu, K.Kato, and J. Kimura, J.Amer.Chem.Soc.,91,6510(1969); (b)O.Mitsunobu, M.Wada, and T.Sano, ibid.,94,679(1972); (c)M.Wada, T.Sano, and O.Mitsunobu,Bull.Chem.Soc.Japan, 46,2833(1973); (d)M.Wada and O.Mitsunobu, Tetrahedron Lett.,1279(1972); (e)O.Mitsunobu and M.Eguchi,Bull.Chem.Soc.Japan,44,3427(1971).