DECOMPOSITION OF 5'-METHYLTHIOADENOSINE

Theodore F. Lavine, Norman F. Floyd and Mary S. Cammaroti

The Institute for Cancer Research
Philadelphia, Pa.

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It has long been known that 5-methylthioribose and 5'-methylthioadenosine yield low results in the Zeisel methoxyl procedure (Suzuki and Mori, 1925) because of the concomitant formation of methyl mercaptan (Kuhn, Birkofer and Quackenbush, 1939). This behavior apparently furnishes a striking example of a difficulty often encountered in the analysis of S-methyl compounds, namely, that cleavage by hydriodic acid may occur in either of two ways: $CH_3SH + RI \longleftarrow (RS(H)CH_3)^+I^- \longrightarrow RSH + CH_3I$. We have been investigating a means of overcoming this difficulty by incorporating an alkylating agent in the digestion mixture. This creates forcing conditions for the elimination of methyl iodide by the in situ formation of a sulfonium salt that subsequently decomposes, as follows, $RSCH_3 + R'I \longrightarrow (RS(R')CH_3)^+I^- \longrightarrow RSR' + CH_3I$. Provided a high iodide concentration is maintained, the reaction proceeds as well in dilute as in the usual azeotropic acid and by the proper choice of conditions O-methyl, S-methyl and sulfonium methyl groups may be differentiated. The scope and limitations of the method will be described elsewhere. In view of the current interest in the chemical and biological behavior of S-adenosylmethionine, we are motivated to make a preliminary report of our findings with 5'-methylthioadenosine which we interpret as indicating migration of the S-methyl group from the 5-position to the aldehydic carbon of ribose.

As shown in Table I, substantially quantitative results for methyl iodide were obtained with 5'-methylthioadenosine[1] on refluxing in 7 M NaI in the

[1] Kindly supplied by Dr. F. Schlenk, Argonne National Laboratory. Oxidation by KIO_3 in N HCl yielded mol. wt. 283 on the basis of sulfoxide formation; theory, 293.

Table I

Decomposition of S-Alkyl Ribose Derivatives

(Reaction time, 2 hrs. Results are expressed as % of theory)

	5'-Methylthio-adenosine		D-Ribose diisobutyl mercaptal	
Digestion Mixture[a]	CH_3I[b]	CH_3SH[c]	iso-BuI[b]	iso-BuSH[c]
7 M NaI, RI[d]	95.7	3.9	4.0	90.7
1 M HI, 6 M NaI	43.2	54.9	---	----
1 M HI, 6 M NaI, RI[d]	61.5	31.0	2.4	88.6

[a] Contains 0.1 M H_3PO_2 and 0.03-0.05 millimole of sulfur compound in 11 ml. of digestion mixture.

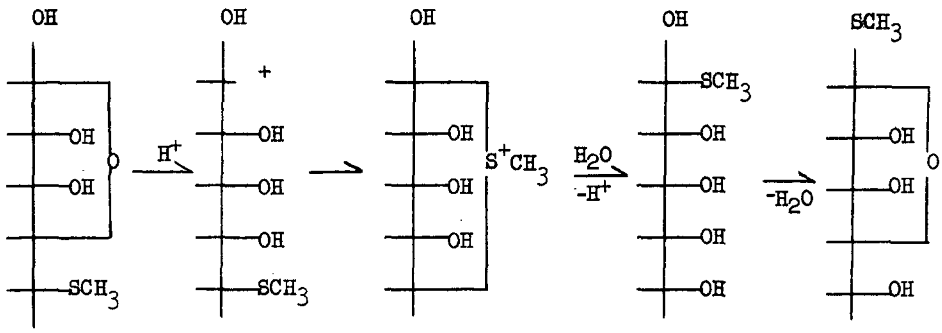
[b] Br_2-acetic acid - acetate trap.

[c] Saturated aqueous $HgCl_2$ trap and/or trap containing 0.02 N KIO_3 in N HCl; SH was determined by oxidation to SS ($HgCl_2$ trap) or to SO_3H (KIO_3 trap). Order of absorption train(1) 20% $BaCl_2$, 20% $CdCl_2$, 15% KI,(2) $HgCl_2$, (3) KIO_3,(4) Br_2 - acetic acid.

[d] 0.2 gm. β-iodopropionic acid.

presence of β-iodopropionic acid. This is normal behavior for a thioether structure. In 1 M HI, somewhat more than half the S-methyl groups are liberated as methyl mercaptan. The reaction is rapid, being essentially complete in 1 hr. The methyl mercaptan formation although reduced, was not eliminated as expected by the addition of β-iodopropionic acid to the acid mixture. In light of the fact that D-ribose diisobutyl mercaptal (m.p. 85°C. uncor.; Zinner, 1950, reports m.p. 83.5-84°C.) essentially cleaves to yield only the mercaptan under all conditions, it would appear that a methyl hemimercaptal or methylthio riboside is being formed in acid solution. This is rendered plausible because of the pronounced tendency of ribose and N-ribosides to exist in a variety of tautomeric forms which arise from equilibria between furanose, pyranose and aldehydic structures (Jeanloz and Fletcher, Jr., 1951; Overend and Stacey, 1955). Under the present conditions (i.e. boiling 1 N acid, cf. Parks and Schlenk, 1958) it is likely that the N-glycosidic

bond is cleaved and, accordingly, the rearrangement may be represented in terms of ribose, as follows:



Such a change may account for the slow response of 5'-methylthioadenosine to the orcinol test (Baddiley, Cantoni and Jamieson, 1953) and would furnish an easy path for the biological cleavage of homocysteine from S-adenosyl homocysteine. In any event, the possibility of such a rearrangement should be considered when ribose derivatives are subjected to acid conditions.

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