Organic Mass Spectrometry, 1968, Vol. 1, pp. 205 to 214. Heyden & Son Limited. Printed in Northern Ireland

ORGANIC MASS SPECTROMETRY—X*.

ELECTRON IMPACT FRAGMENTATIONS OF ALKYLTHIO GROUP IN 2-ALKYLTHIO-5-AMINOTHIAZOLO[5,4-d] PYRIMIDINES

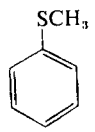
A. TATEMATSU, S. SUGIURA, S. INOUE
Faculty of Pharmacy, Meijo University, Showa-ku, Nagoya
and
T. GOTO
Faculty of Agriculture, Nagoya University, Chikusa-ku, Nagoya

(*Received* 18 *December* 1967; *accepted* 1 *January* 1968)

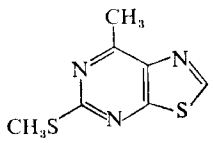
Abstract—In order to discuss hydrogen transfer in the skeletal fragmentation of thioethers on electron impact, mass spectra of a series of 2-*n*-alkylthio-5-aminothiazolo[5,4-d]pyrimidines have been determined. To aid the interpretation of the hydrogen migration, deuterium-labeled compounds which are substituted with deuterium in each position of 2-*n*-butylthio-5-aminothiazolopyrimidines were studied. By correlation of the spectra obtained from such labeled compounds, the initial hydrogen migration in the fragmentation to produce [M − SH], [MS − CH_3] and *m/e* 184 ions is concluded to be as follows: migration of the α-hydrogen atom to the sulfur induces formation of the [M − SH] ion; migration of the β-hydrogen atom to the sulfur or nitrogen atom by a McLafferty rearrangement induces formation of the *m/e* 184 ion; and migration of γ-hydrogen atom to the sulfur induces formation of the [M − SCH_3] ion.

UPON electron impact thioethers undergo interesting skeletal rearrangements with the expulsion of S, SH, etc. from the molecular ion.[2]

Methyl phenyl sulfide (I), for example, gives a strong M-33 [M − SH] peak in its mass spectrum.[3] In this case, the hydrogen atom eliminated with the sulfur originates mainly from the methyl group (69%); the remainder being provided from the aromatic protons, possibly from the ortho positions.[3] 5-Methylthio-7-methylthiazolo[5,4-d]pyrimidine (II) has no hydrogen atoms in ortho positions of the methylthio group, and hence the hydrogen atom eliminated with the sulfur originates entirely from the methyl group (Table 1).



I

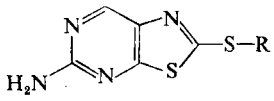


II

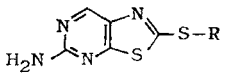
In the mass spectra of a series of 2-*n*-alkylthio-5-aminothiazolo[5,4-d]pyrimidines (III–X) (Fig. 1), the following characteristic features are observed.

(1) α-Cleavage and carbon–sulfur cleavage, which are observed as major fragmentations in dialkyl sulfides[4] and the former in phenyl alkyl sulfides,[3b] are not important in this series.

* Organic Mass Spectrometry. Part X: Preceding paper, Part IX, S. Ukai *et al.*[1]



R = CH_3	(III)
R = C_2H_5	(IV)
R = *n*-C_3H_7	(V)
R = *n*-C_4H_9	(VI)
R = *n*-C_5H_{11}	(VII)
R = *n*-C_6H_{13}	(VIII)
R = *n*-C_8H_{17}	(IX)
R = *n*-$C_{10}H_{21}$	(X)



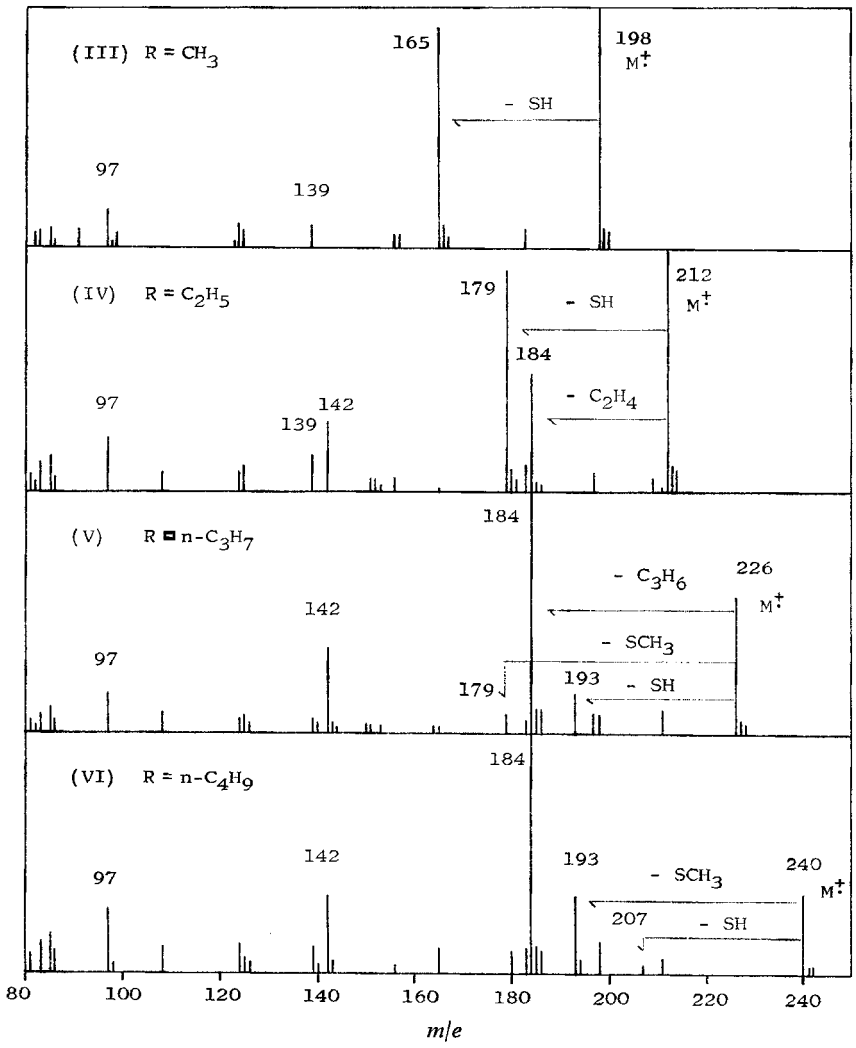
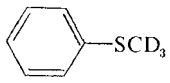
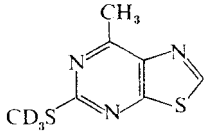
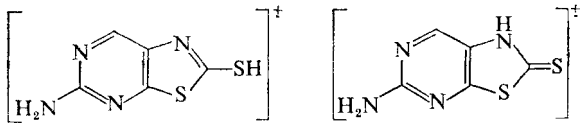


FIG. 1. Mass spectra of 2-alkylthio-5-aminothiazolo[5,4-d]pyrimidines (III–VI).

TABLE 1. COMPOSITIONS OF M-33 ION IN THE MASS SPECTRA OF DEUTERATED ANALOGS OF METHYL PHENYL SULFIDE (I) AND 5-METHYLTHIO-7-METHYLTHIAZOLO[5,4-D]PYRIMIDINE (II).

	[M − SH]	[M − SD]
	31%	69%
	~0%	~100%

(2) Olefin elimination forming the mercaptan ion *a* (*m/e* 184; or possibly involving a McLafferty rearrangement leading to *a'*) is also one of the important fragmentations in the case of dialkyl sulfides[4] and alkyl phenyl sulfides.[4b]



a *a'*

m/e 184 ion

(3) In the case of alkyl phenyl sulfides,[3b] the skeletal rearrangement peak, [M − SH], is only important in the spectrum of the methyl derivative, whereas the [M − SH] peak and another skeletal rearrangement peak, [M − SCH_3] are fairly important in the spectra of the 2-*n*-alkylthio-5-aminothiazolopyrimidines (IV–X) having the alkyl group greater than methyl.

(4) When the alkyl group becomes greater than ethyl, the intensity of the [M − SH] peak decreases markedly and instead there appears the [M − SCH_3] peak, the intensity of which becomes maximal in the spectrum of the *n*-butyl derivative (VI).

(5) The *m/e* 184 peak, *a* or *a'*, which is formed by elimination of the alkyl group from the molecular ion with migration of a hydrogen atom, is not observed in the spectrum of the methyl derivative (III), but becomes fairly intense in the spectrum of the ethyl derivative (IV) and reaches near maximal intensity in the spectra of the *n*-propyl derivative (V) and higher homologs (VI–X).

These three rearranged ions, [M − SH], [M − SCH_3], and *m/e* 184, are formed directly from the molecular ion, since the appropriate metastable peaks are observed. Since the simultaneous formation of an aromatic-alkyl bond with elimination of the SH or SCH_3 radical directly from the original molecular ion is impossible, initial

hydrogen migration from the alkyl group to the sulfur atom in the side chain must be involved.

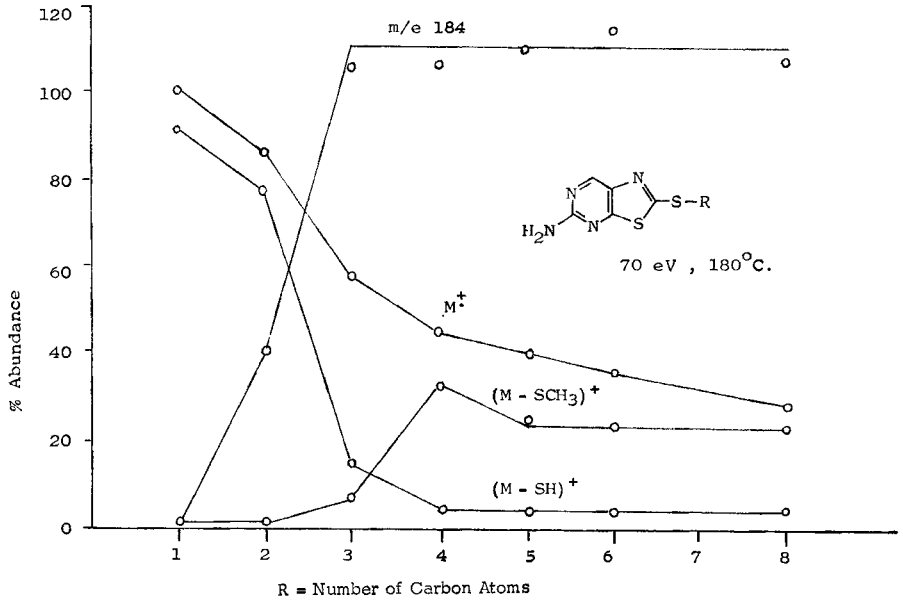
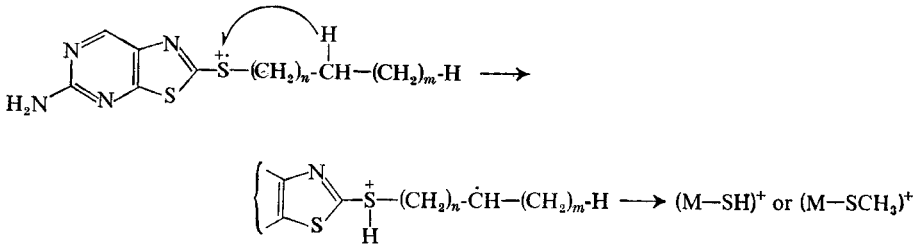


FIG. 2. Dependence of abundance of the three rearrangement ions on the length of alkyl-chain in 2-*n*-alkylthio-5-aminothiazolo[5,4-d]pyrimidines. (Intensity of the molecular ion of 2-methylthio derivative is used as an internal standard and taken as 100%.)

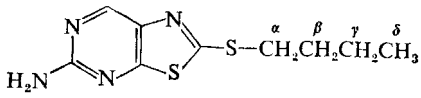


Consideration of the fact that secondary hydrogen atoms are more prone to migrate than primary hydrogens,[4b] the following assumptions can be drawn from inspection of the results shown in Fig. 2.

Migration of the α-hydrogen atom to the sulfur induces formation of the [M − SH] ion; migration of the β-hydrogen atom to the sulfur or nitrogen atom by a McLafferty rearrangement induces formation of the *m/e* 184 ion; and migration of γ-hydrogenatom to the sulfur induces formation of the [M − SCH_3] ion.

To confirm the above assumptions we prepared the complete series of side-chain deuterium-labeled 2-*n*-butylthio-5-aminothiazolopyrimidines (XI–XIV) and measured their mass spectra (Table 2).

TABLE 2. PRINCIPAL PEAKS ABOVE *m/e* 183 IN THE MASS SPECTRA OF 2-*n*-BUTYLTHIO-5-AMINOTHIAZOLO[5,4-D]PYRIMIDINE (VI) AND ITS DEUTERATED ANALOGS.*



	no-d	α-d_2	β-d_2	γ-d_2	δ-d_3
Compds.	VI	XI	XII	XIII	XIV
D content		d_2: 94·9%	d_2: 97·1%	d_2: 97·4%	d_3: 87·2%
m/e 243	1·0	5·0	10·0	6·2	34·0
242	3·7	34·8	66·0	39·5	3·5
241	5·0	1·5	2·8	2·5	2·5
240 [$M^{+\cdot}$]	33·8	0·8	0·6	0·1	3·0
213	1·1	3·9	14·6	2·3	1·8
212	1·9	0·6	1·0	2·3	2·1
211 [M − C_2H_5]	7·0	0·8	1·1	10·5	8·0
210	0·1	1·0	2·1	1·2	4·9
209	1·2	2·1	6·0	6·3	3·1
208	1·0	1·0	2·2	1·0	0·1
207 [M − SH]	4·4	0·5	0·5	0·1	1·5
200	2·0	7·4	3·1	2·5	3·0
199	2·2	2·9	4·0	14·5	3·8
198 [M − C_3H_6]	13·0	0·8	29·0	2·0	14·2
197	3·9	0·5	10·3	4·8	8·0
196	0·1	0·5	8·8	2·6	31·0
195	2·1	2·5	72·0	4·9	3·0
194	4·7	4·7	2·1	23·0	1·2
193 [M − SCH_3]	33·0	36·9	1·7	1·0	1·0
186	9·9	10·0	16·7	12·0	11·7
185	11·8	15·7	100·0	28·8	17·2
184 [M − C_4H_8]	100·0	100·0	69·4	100·0	100·0
183	10·6	9·9	19·0	12·9	19·0

* Uncorrected for natural abundances.

From these results the following conclusions can be drawn:

(1) Hydrogen atoms in the SCH_3 radical eliminated from the molecular ion originate entirely from the two α-hydrogens and one of the γ-hydrogens, indicating that firstly one of the γ-hydrogen atoms migrates to the sulfur and then this SH and the α-CH_2 group are eliminated as the $HSCH_2\cdot$ radical.

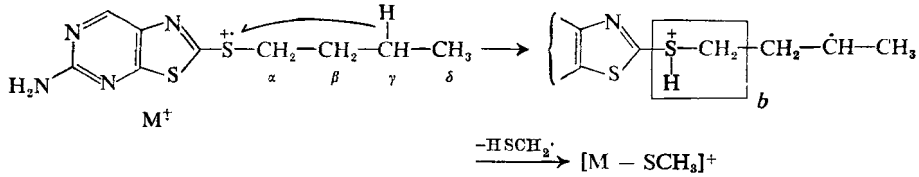
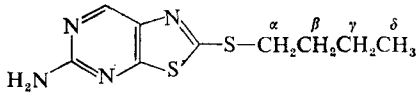


TABLE 3. SOURCE OF HYDROGEN ATOMS THAT ARE ELIMINATED AS SH· AND SCH_3· FROM THE MOLECULAR ION WITH PRODUCTION OF SKELETAL REARRANGEMENT IONS $[M - SH]^+$ AND $[M - SCH_3]^+$, RESPECTIVELY*.

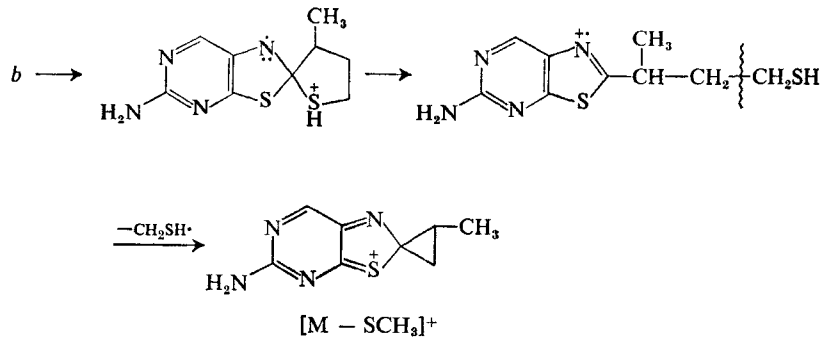


	SH·†	SCH_3·
α	33–39%	98·6% (2H)
β	27–35	4·2
γ	8–10	93·1 (1H)
δ	31–41	7·9

* Corrected for natural abundances.

† The *m/e* 209 ion with uncertain composition interfere the accurate calculations. Estimated upper and lower limits are shown.

The skeletal rearrangement processes may be explained as shown below.



$[M - SCH_3]^+$

(2) The hydrogen atom in the SH radical that is eliminated to produce the [M — SH] ion comes mainly from the α-, β- and δ-positions but is less likely from the γ-position. This type of hydrogen transfer may be non-specific and the decrease in migration from the γ-position may be attributed to the presence of the competing fragmentation in the production of the [M — SCH_3] ion, which is initiated exclusively by the γ-hydrogen migration shown above. From the mechanistic point of view discussed in a previous paper,[3a] the immediate precursor of the bond formation between the aromatic and alkyl moieties is possibly the α-carbon radical *c* illustrated below. Thus, initial migration of the β- or δ-hydrogen atom to the sulfur may be followed by the migration of α-hydrogen atom to the vacant β- or δ-position to produce ion *c*.

(3) The hydrogen atom that migrates to produce the *m/e* 184 ion is mainly from the β-position (57%) and γ-hydrogen contributes only to the extent of 16%. Hydrogen atom contributions from other positions are small (Table 4). The sum of deuterium migration in each position is only 85%. This low value may be attributable to the D–H isotope effect.[5]

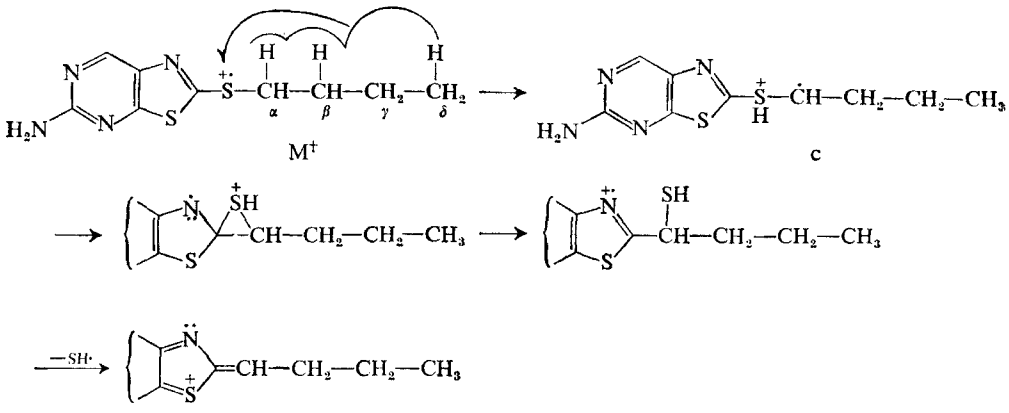
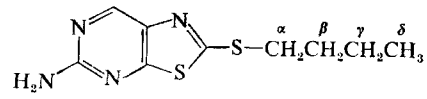


TABLE 4. COMPOSITIONS OF [M — ETHYL]$^+$, [M — PROPYLENE]$^{+\cdot}$, AND [M — BUTYLENE]$^{+\cdot}$ IONS IN THE MASS SPECTRA OF DEUTERATED ANALOGS OF 2-*n*-BUTYLTHIO-5-AMINOTHIAZOLO-[5,4-D]PYRIMIDINE (VI).*



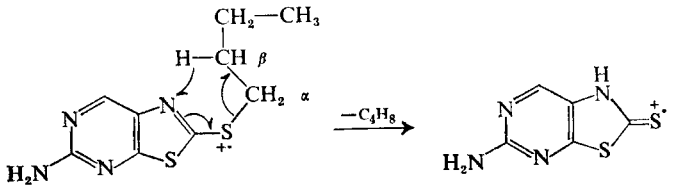
	[M — Ethyl]$^+$		[M — Propylene]$^{+\cdot}$		[M — Butylene]$^{+\cdot}$ †	
α-d_2	[M — C_2H_5]	75·9%	[M — C_3H_6]	85·0%	[M — $C_4H_6D_2$]	93·9%
β-d_2	[M — C_2H_5]	86·8	[M — $C_3H_4D_2$]	96·7	[M — $C_4H_6D_2$]	42·6
					[M — C_4H_7D]	57·4
γ-d_2	[M — $C_2H_3D_2$]	96·0	[M — C_3H_5D]	93·1	[M — $C_4H_6D_2$]	84·1
					[M — C_4H_7D]	15·9
δ-d_3	[M — $C_2H_2D_3$]	91·5	[M — $C_3H_3D_3$]	97·5	[M — $C_4H_6D_2$]	94·2

* Corrected for natural abundances.

† [M — Butylene]$^{+\cdot}$ ion corresponds to *m/e* 184 ion.

MacLeod and Djerassi observed[5] that in the spectrum of phenyl *n*-butyl sulfide the extent of hydrogen transfer from the β-position (19%) is smaller than that observed in the spectrum of the corresponding ether (25%), even although in the latter case the hydrogen transfer is mostly non-specific. They attributed this result to suppression of the contributing McLafferty rearrangement species in the sulfide, due to the greater charge-stabilizing ability of the sulfur. Thus, contrary to the case of phenyl *n*-butyl sulfide, highly specific β-hydrogen transfer observed in the case of 2-*n*-butylthio-5-aminothiazolopyrimidine (VI) indicates that this rearrangement occurs mostly through the McLafferty type six-membered transition state *d* involving a nitrogen atom (this could be attributed to the preference of the McLafferty rearrangement over the hydrogen transfer from the β-position to the sulfur atom via a four-membered cyclic transition state).

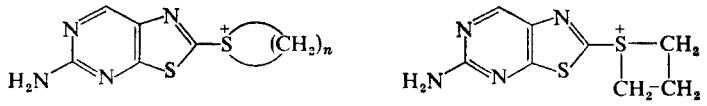
Another interesting feature is that a series of M-alkyl peaks is observed in the spectra of *n*-alkylthio derivatives (VI–X), although their intensity is not high (Table 5).



d a'

Amongst the possible [M — R] ions peaks for which $n = 0, 1, 2, 4, 5$ appear with similar intensities, whereas the peak for $n = 3$ cannot be detected (intensities are comparable to the blank values).

These results suggest that the fragment ions involve cyclic structures such as *e* and that the four-membered cyclic structure (*f*) is too unstable to exist. Cyclic structures larger than six-membered ($n > 5$) are also unfavorable. Similar results are also reported in the case of aliphatic thiols.[4a]



e n=2, 4, 5 *f*

EXPERIMENTAL

The mass spectra were measured by Hitachi RMU-6E type double-focussing mass spectrometer, using an all-glass heated inlet system. The ionizing energy was kept at 70 eV, and the ionizing current at 80 μA.

1-(2′-*tetrahydropyranoxy*)*butan*-3-*one* (*XV*). A mixture of acetylethanol (18 g) and 2,3-dihydropyran (17·8 g) containing one drop of conc. HCl was kept overnight at room temp., then diluted with ether (350 ml), and neutralized with 10% NaOH. The ether layer was washed with H_2O and dried over Na_2CO_3. Removal of the solvent left 34·9 g of an oily product which was purified by the usual distillation; colorless oil, b.p. 104–105° (12 mm), yield, 28·4 g (*Anal.*: Calcd. for $C_9H_{16}O_3$: C, 62·76; H, 9·36. Found: C, 62·57; H, 9·60%.)

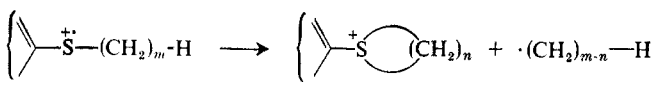
1-(2′-*tetrahydropyranoxy*)*butan*-3-*ol*-3-*d* (*XVI*). To a suspension of 3 g of $LiAlD_4$ in 200 ml of ether was added dropwise a solution of 14·1 g of (XV) in 42 ml of ether. After stirring was continued for 4 hours under reflux, the resulting reaction complex and the excess of hydride were decomposed by adding a saturated NH_4Cl solution. After separation of the ether phase, the aqueous layer was extracted with ether and the combined ether extract dried and evaporated to give a crude oily product of (XVI). Vacuum distillation of the crude oil provided 12 g of colorless oil, b.p. 104–105° (6 mm). (*Anal.*: Calcd. for $C_9H_{16}O_3D_2$: C, 62·07; H(D), 10·34. Found: C, 61·67; H(D), 10·55%.)

1-(2′-*tetrahydropyranoxy*)*butan*-3-*ol*-3-*d p-toluenesulfonate* (*XVII*). To a solution of 10 g of (XVI) in 70 ml of pyridine was added 11·9 g of TsCl with stirring and the reaction mixture was kept at room temp. for 2 hours. The excess of pyridine was removed at room temp. under vacuum, and the residue was taken up in ether. From the ether solution, there was obtained 15·8 g of a pale yellow oily product. This product was used for further reactions without purification.

1-(2′-*tetrahydropyranoxy*)*butane*-3,3-d_2 (*XVIII*). Reduction of 7·8 g of the tosylate (XVII) with 2 g of $LiAlD_4$ was done in the same way as described in the case of (XVI), and the product (XVIII) boils at 53–54° (6 mm). Yield, 2·8 g.

1-*bromobutane*-3,3-d_2 (*XIX*). After stirring of a solution of 3 g of (XVIII) in 15 ml of 20% H_2SO_4 for one hour, the resulting reaction mixture was distilled, and the butanol in the distillate was extracted with CH_2Cl_2 and the extract dried over Na_2SO_4. On removal of the solvent an oily product remained which was fractionated and the distillate at 105–106° was collected (1 g). The butanol thus obtained was brominated in the usual manner (NaBr + H_2SO_4) to give 0·47 g of 1-bromobutane-3,3-d_2 (XIX) (b.p. 114–115°).

TABLE 5. RELATIVE ABUNDANCES OF FRAGMENT IONS PRODUCED BY ELIMINATION OF ALKYL RADICALS IN THE MASS SPECTRA OF 2-N-ALKYLTHIO-5-AMINOTHIAZOLOPYRIMIDINES.



m \ *n*	0	1	2	3	4	5	6	7	8	9
	$-S^+$	$-\overset{+}{S}=CH_2$	$-\overset{+}{S}(CH_2)_2$	$-\overset{+}{S}(CH_2)_3$	$-\overset{+}{S}(CH_2)_4$	$-\overset{+}{S}(CH_2)_5$	$-\overset{+}{S}(CH_2)_6$	$-\overset{+}{S}(CH_2)_7$	$-\overset{+}{S}(CH_2)_8$	$-\overset{+}{S}(CH_2)_9$
4	10·6	3·9	7·0	0·2						
5	6·8	6·2	5·3	0·3	1·2					
6	5·5	5·3	4·7	0·3	4·3	0·9				
8	15·3	5·4	4·5	0·3	5 4	4·5	0·8	0·3 ·		
10	11·7	7·1	4·0	0·2	5·9	5·0	1·0	0·5	0·5	0·3

2,n-butyl-3',3'-d_2-thio-5-aminothiazolo[5,4-d]pyrimidine (XIII). A mixture of 1·2 g of 2-mercapto-5-aminothiazolopyrimidine[7] (XX) and 0·9 g of (XIX) in 3·6 ml of MeOH containing 0·036 g of KOH was refluxed for 30 minutes. After cooling, the deposited crystals were collected and recrystallized from EtOH to afford 1·2 g of colorless needles, m.p. 157–158°. (*Anal.*: Calcd. for $C_9H_{10}N_4D_2S_2$: C, 44·60; H(D), 4·96. Found: C, 44·50; H(D), 4·73%.) Other 2-*n*-butylthio-5-aminothiazolo-[5,4-d]pyrimidines containing 1',1'-d_2 (XI), 2', 2'-d_2 (XII), and 4',4',4'-d_3 (XIV) were prepared by essentially the same method from (XX) and the corresponding *n*-butyl bromide containing deuterium atoms at appropriate positions according to the published procedures.[8] For the deuterium contents of these compounds, see Table 2.

REFERENCES

1. S. Ukai, K. Hirose, A. Tatematsu and T. Goto, *Tetrahedron Letters* 4999 (1967).
2. For reviews, *a.* H. Budzikiewicz, C. Djerassi and D. H. Williams, *Mass Spectrometry of Organic Compounds* Holden-Day, San Francisco. 1967, p. 280; *b.* P. Brown and C. Djerassi, *Angew. Chem. (Int. Ed.)* **6,** 477 (1967).
3. *a.* A. Tatematsu, S. Inoue and T. Goto, *Tetrahedron Letters* 4609 (1966); *b.* J. H. Bowie, S.-O. Lawesson, J. Ø. Madson, G. Schrell and D. H. Williams, *J. Chem. Soc. (B)* 951 (1966).
4. *a.* E. J. Levy and W. A. Stahl, *Anal. Chem.* **33,** 707 (1961); *b.* S. Sample and C. Djerassi, *J. Am. Chem. Soc.* **88,** 1937 (1966).
5. J. K. MacLeod and C. Djerassi, *J Am. Chem. Soc.* **88,** 1840 (1966).
6. J. T. Hays, C. F. Hager, H. M. Engelman, and H. M. Spurlin, *J. Am. Chem. Soc.* **73,** 5369 (1951).
7. S. Sugiura, E. Suzuki, T. Naito and S. Inoue, *Chem. Pharm. Bull.* (1967) in press.
8. *a.* D. H. Williams, H. Budzikiewicz and C. Djerassi, *J. Am. Chem. Soc.* **86,** 284 (1964); *b.* E. Cerwonka, R. C. Anderson and E. V. Brown, *J. Am. Chem. Soc.* **75,** 30 (1953); *c.* A. M. Duffield, R. Bewgelmans, H. Budzikiewicz, D. A. Lightner, D. H. Williams and C. Djerassi, *J. Am. Chem. Soc.* **87,** 805 (1965).