ORGANOGERMANIUM COMPOUNDS : FIRST GENERAL METHODS FOR SYNTHESIS OF BIOACTIVE TRITHIAGERMATRANES WITH NOVEL FUNCTIONAL GROUPS

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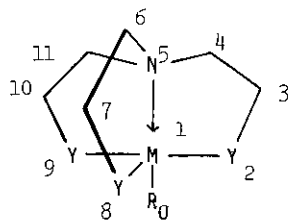
Abstract —— The first general methods for the synthesis of 1-substituted trithiagermatranes (3) have been developed using the reaction of tris-(2-mercaptoethyl)amine with trimethoxygermyl compounds (5), sesquioxides (6) and sesquisulfides(7). These newly prepared compounds were found to have the capacity to relieve pain, thus indicating them to have strong inhibitory activity toward a decomposition enzyme for enkephalin which is an opioid peptide in a living body.

Silatranes (1) as compounds with metalatrane skeletons[1] are attraction of much attention in view of their high biological activity and peculiar chemical structures[2]. Their biological activity depends to a considerable degree on the particular substitute bounded to the metal. Similar compounds such as germatranes (2) can be formed by replacing silicon with germanium. There are not many reports of synthesis and physiological activities of such compounds[3]. We submitted our own report of simple methods for the synthesis of 1-substituted germatranes[4]. On the other hand, Lukevits et al.[5] have recently reported carbamoylgermatrane (2)(Ro = $CH_2CH_2CONH_2$) to have psychotropic and antitumor activity. It has been also reported that 2-ethoxycarbonylgermanium sesquioxide[6], now being developed as antitumor agent of biological response modifies (BRM) type, decreased the pain caused by carcinomas in clinical studies[7] and showed inhibitory action against enkephalin-degrading enzymes[8].

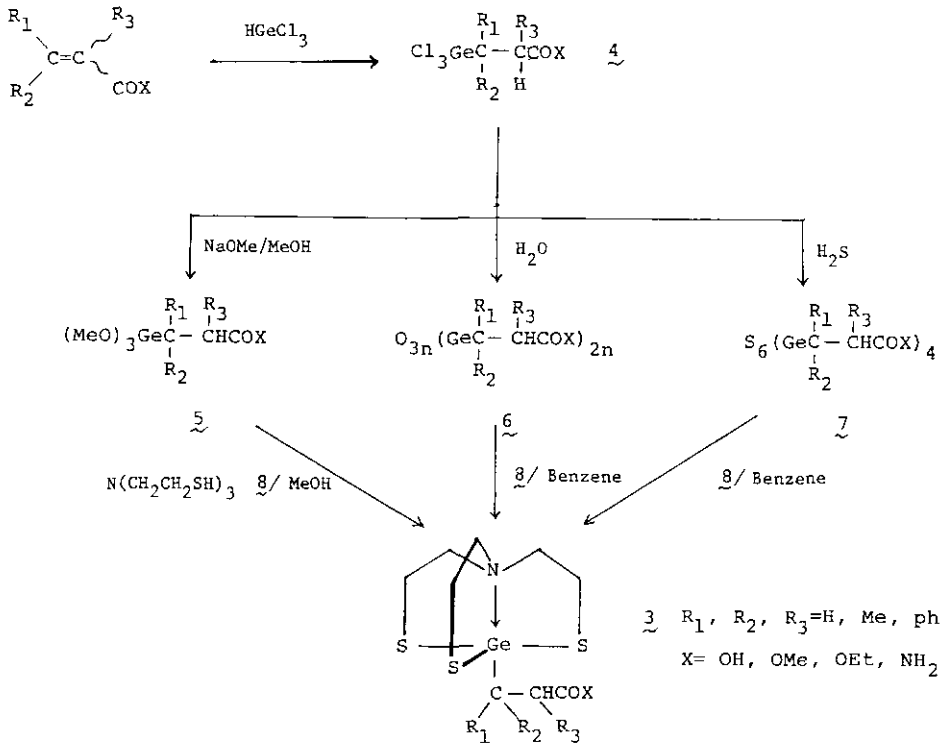


1 Y=O, M=Si

2 Y=O, M=Ge

3 Y=S, M=Ge

In a research for the potent organogermanium compounds having biological activities than above compounds, we wish to report here first convenient synthesis and bioactivities of trithiagermatranes (3) replaced oxygen of trioxagermatranes with sulfur. The compounds (3) were prepared according to each of the following three methods shown in Scheme 1. First, α, β-unsaturated compounds reacted with trichlorogermane to form trichlorogermyl adducts (4)[9], which in turn reacted with NaOMe to yield trimethoxygermyl derivatives (5). These derivatives, unisolated, were combined with tris(2-mercaptoethyl)amine in methanol to provide 2,8,9-trithiagermatranes (3) in moderated yields (Method A). Secondly, tris(2-mercaptoethyl)amine and germanium sesquioxides (6)[9] obtained from the hydrolysis of germyl adducts (4) were heated in benzene to form the compounds (3)(Method B). Thirdly, compounds (4) reacted with H_2S to form germanium sesquisulfides (7)[10], which were then combined with tris(2-mercaptoethyl)amine to give the compound (3)(Method C). Method A and B were similar to the method for the synthesis of oxagermatranes, except that tris(2-mercaptoethyl)amine was used instead of triethanolamine. Method C was found to give better results than Method B.



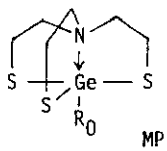
Scheme 1

Trithiagermatrane could be produced by each of the above three methods but method C to be the best. Method A was inadequate, particularly when Ro reacted with NaOMe such as a carboxyl or hydroxyl group. The sesquisulfide (7) in Method C was much more soluble in the reaction solvent than sesquioxide (6) in Method B, so that Method C could be carried out more easily, as evident from the following examples.

1-Methyl-2-carboxyethylgermanium sesquisulfide (7b, $R_1 = CH_3$, $R_2 = R_3 = H$)(2.2m mol) was added to a solution of tris(2-mercaptoethyl)amine (8)(1.75g, 8.8m mol) in a dry benzene solvent (30 ml), followed by heating and then refluxing for 5h. The solvent was distilled to give crystals. 3-(1'-Germa-5'-aza-2', 8', 9'-trithia-bicycloundecyl)3-methylpropanoic acid (3b)(2.4g), a needle-like crystalline solid, mp 175°C, was obtained in a 77.1% yield by recrystallization in acetone. Anal. Caldc. for $C_{10}H_{19}GeNO_2S$: C, 33.93; H, 5.41; N, 3.95; Ge, 20.51. Found : C, 34.02; H, 5.43; N, 3.96; Ge, 20.48. IR ν_{max}^{KBr} cm^{-1} : 1700 (X=O), 400, 380 (Ge-S). ^{1}H-NMR (Acetone-d_6, δ, ppm) : 1.17 (3H, d, J=7.0Hz, CH_3), 1.4-1.9 (1H, m, CH), 2.16, 2.75 (2H, dd, CH_2), 2.73 (4H, m, N-CH_2CH_2-S), ^{13}C-NMR (DMSO-d_6, δ, ppm) : 13.29 (CH_3), 21.42 (N-C), 29.62 (Ge-C), 34.88 (CH_2), 51.27 (S-C), 171.51 (CO), MS m/z : 356 (M^+).

The molecular structure of the trithiagermatranes (3) thus obtained was determined by elemental analysis and data from spectral analysis, such as IR, ^{1}H-NMR, ^{13}C-NMR and mass spectroscopy. The results are presented in Table I and II.

Table I Synthesis of 2, 8, 9-trithiagermatrane (3)

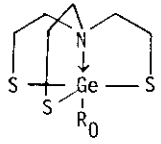


$R_0 = C(R_1)(R_2) - CH(R_3) - C(=O)X$ X = OH, NH_2, OMe, OEt

3	R_1	R_2	R_3	X	MP (°C)	Reaction Conditions: Solvent	Temp.(°C)	Time(h)	Method & Yield %	Molecular fomula*
a	H	H	H	OH	167	C_6H_6	reflux	5	(B) 51.0	$C_9H_{17}GeNO_2S_3$
b	CH_3	H	H	OH	175	C_6H_6	reflux	6	(C) 77.1	$C_{10}H_{19}GeNO_2S_3$
c	H	H	CH_3	OH	135	C_6H_6	reflux	6	(C) 52.0	$C_{10}H_{19}GeNO_2S_3$
d	CH_3	H	CH_3	OH	133	C_6H_6	reflux	10	(C) 46.6	$C_{11}H_{22}GeNO_2S_3$
e	CH_3	CH_3	H	OH	148	C_6H_6	reflux	4	(C) 54.0	$C_{11}H_{22}GeNO_2S_3$
f	C_6H_5	H	H	OH	198	C_6H_6	reflux	10	(C) 84.0	$C_{15}H_{21}GeNO_2S_3$
g	C_6H_5	H	CH_3	OH	121	C_6H_6	rellux	10	(C) 72.0	$C_{16}H_{23}GeNO_2S_3$
h	H	H	H	NH_2	194	C_6H_6	reflux	2	(A) 44.8	$C_9H_{18}GeN_2OS_3$
i	C_6H_5	H	H	NH_2	203	C_6H_6	reflux	6	(B) 70.0	$C_{15}H_{22}GeN_2OS_3$
j	H	H	H	OCH_3	87	EtOH	reflux	10	(A) 61.2	$C_{10}H_{19}GeNO_2S_3$
k	C_6H_5	H	H	OC_2H_5	105-107	EtOH	reflux	10	(A) 56.3	$C_{17}H_{25}GeNO_2S_3$

* Elemental analyses of the compounds were in satisfactory agreement with the calculated values.

Table II Spectroscopic data of 2, 8, 9-trithiagermatranes (3)



$R_0 = \begin{matrix} R_1 \\ | \\ C - CH - C = O \\ | \quad | \quad | \\ R_2 \quad R_3 \quad X \end{matrix}$ X = OH, NH_2, OMe, OEt

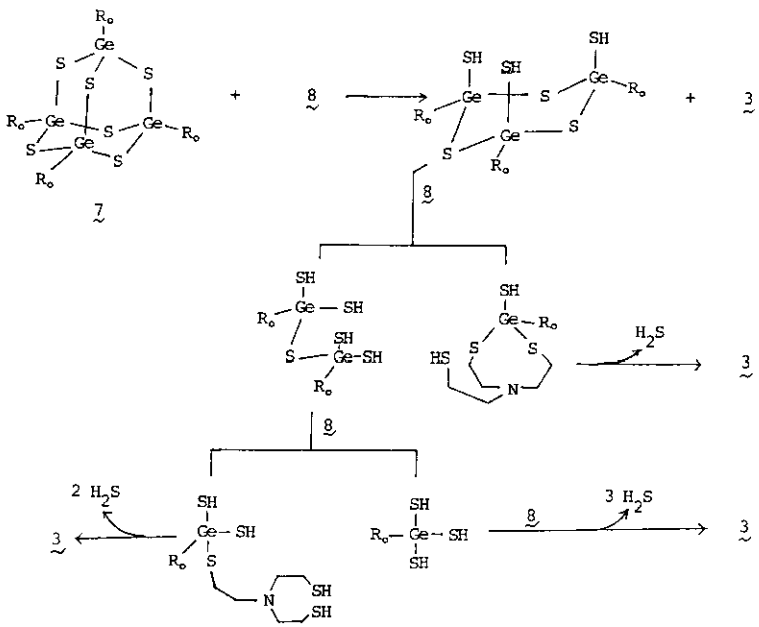
3	IR (cm^{-1}) C=O	Ge-S	solvent $^{13}C/^{1}H$	N-C 3x2H	S-C 3x2H	C-1 1H or 2H	C-2 1H or 2H	1-Me(Ph) 3H or 5H	2-Me 3H	1,1-Me 2x3H	C-3 X	MS(M^+) m/z
a	1700	400,370	$CDCl_3$	25.49	55.73	24.65	29.72				180.07	342
			$CDCl_3$	2.70(s)	2.70(s)	1.46(t)J9.0	2.58(t)J9.0				OH	
b	1700	400,380	d-6 DMSO	21.42	51.27	29.62	34.88	13.29			171.51	356
			$(CD_3)_2CO$	2.73(s)	2.73(s)	1.4 1.9(m)	2.16,2.75 i*	1.17(d)J7.0			OH	
c	1700	400,380	$CDCl_3$	25.88	55.86	34.40	36.35		19.57		183.39	356
			$CDCl_3$	2.70(s)	2.70(s)	1.35,1.76 ii*	2.6~2.9(m)		1.28(d)J7.0		OH	
d	1700	390	$CDCl_3$	26.27	56.71	39.15	43.12	14.89	17.36		182.41	370
			$CDCl_3$	2.68(s)	2.68(s)	1.80(br,qu)J7.2	2.76(br,qu)J7.2	1.25(d)J7.2	1.33(d)J7.2		OH	
e	1705	405,395	d-6 DMSO	24.71	55.08	36.09	42.27			23.08	172.78	371
			$(CD_3)_2CO$	2.72(s)	2.72(s)		2.48			1.26(s)	OH	
f	1695	400,380	d-6 DMSO	50.78	56.18	36.80	36.54,41.42	Ph*			174.10,174.21	418
			d-6 DMSO	2.63(s)	2.63(s)		2.2~2.8(m)	7.16(br,s)			OH	
g	1700	400,390	d-6 DMSO	25.29	54.82	43.89	54.10	Ph**	19.51		176.56	431
			$CDCl_3$	2.6	2.9(m)		2.36 iii*	7.23(m)	1.50(d)J7.5		OH	
h	1660	395,360	d-6 DMSO	24.06	53.26	30.95	27.05				174.93	341
	1620		d-6 DMSO	2.70(br,s)	2.70(br,s)	1.1 1.3(m)	2.15 2.35(m)				NH_2	
i	1670	395	d-6 DMSO	24.32	53.97	46.17	36.41	Ph***			172.98	415
			d-6 DMSO	2.60(m)	2.60(m)		2.60~2.90(m)	7.13(m)			NH_2	
j	1710	390,360	d-6 DMSO	23.86	53.00	26.14	29.59				173.82	356
			$CDCl_3$	2.70(s)	2.70(s)	2.46(t)J7.5	2.4~2.8(m)				OMe*	
k	1730	400,380	$CDCl_3$	24.49	55.73	45.33	36.09	Ph****			172.46	446
			$CDCl_3$	2.3	2.9(m)		2.03(br,s)	7.20(m)			OEt*	

i* (d,d) J=10.1, 15.3Hz, (d,d) J=3.0, 15.3Hz. ii* (d,d) J=8.5, 13.8Hz, (d,d) J=5.0, 13.8Hz iii* (d,q) J=7.5, 9.2Hz.
OMe* ^{13}C 51.44(CH_3) ^{1}H 2.63 (3H, S, CH_3) OEt* ^{13}C 60.09(CH_2), 14.05 (CH_3), ^{1}H 3.94(2H, qu, J=7.2Hz, CH_2), 1.03(3H, t, J=7.2Hz, CH_3)
Ph* C-i 141.76, 143.58 C-o 128.63, 127.52 C-m 128.04, 128.95 C-p 124.34, 126.35
Ph** C-i 142.15 C-o 128.43 C-m 127.52, 128.82 C-p 125.51 Ph*** C-i 141.44 C-o 127.26 C-m 128.37 C-p 124.86
Ph**** C-i 140.73 C-o 127.66 C-m 128.37 C-p 125.57

The infrared spectrum obtained for substances (3) generally showed typical absorption band at 360cm^{-1} to 405cm^{-1} corresponding to the Ge-S bonding band. The mass spectra generally showed a cleavage pattern of M^+ -Ro, M^+ -CH_2CH_2S , M^+ -$CH_2CH_2$2S -$CH_2$2S , M^+ -CH_2CH_2S -CH_2S -CH_2CH_2S , and M^+ -CH_2S , M^+ -CH_2S-CH_2CH_2S , M^+ -CH_2S-2CH_2CH_2S in addition to that of M^+. The reaction of germanium sesquisulfide (7) with tris(2-mercaptoethyl)amine (8) appeared to proceed as follows.

$$\underset{7}{(GeRo)_4S_6} + 4\underset{8}{N(CH_2CH_2SH)_3} \longrightarrow 4\underset{3}{N(CH_2CH_2S)GeRo} + 6H_2S$$

As the compound (7) apparently has the structure tetragermahexathiaadamantane (7)[10], the fragmentation reaction of (7) with tris(2-mercaptoethyl)amine proceeds step-wise to give trithiagermatrane (3) and H_2S as shown in Scheme 2.



Scheme 2

Among these compounds, 3-(1'-germa-5'-aza-2', 8', 9'-trithiabicycloundecyl)propanoic acid (3a) exhibited the inhibitory action against dipeptidyl carboxypeptidase degrading enkephalins that have morphine-like action. These results suggest that this compound may be same effective in physiological pain-regulation system in vivo. Investigation of the other biological activities of these newly prepared compounds is now being carried out.

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