ORGANOGERMANIUM COMPOUNDS: SYNTHESIS, STRUCTURE, AND PROPERTIES OF MASKED-CARBOXYETHYLGERMANIUM SESQUIOXIDE (GE-132) AND RELATED COMPOUNDS WITH ONE TRIETHANOLAMINE COMPONENT

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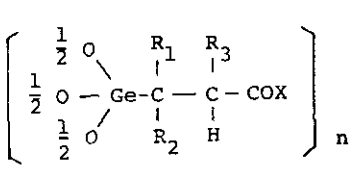
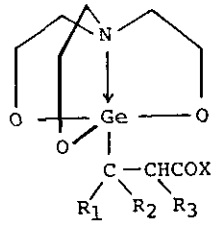
Abstract —— The synthesis, structure, and properties of masked-carboxyethylgermanium sesquioxide (Ge-132) and related compounds with one triethanolamine component were investigated. The hydrolysis of these compounds afforded triethanolamine and trihydroxygermylpropanoic acid derivatives which are important for their biological activity.

The great and ever-increasing interest in metallatrane compounds[1] stems not only from their unique cage structures and physical and chemical properties but as well from the specific biological activity of a number of them. It is of particular interest that Lukevits et al[2] recently reported carbamoylethylgermatrane (4g : R_1=R_2=R_3=H, X=NH_2) to have psychotropic and antitumor activities. We previously observed that carboxyethylgermanium sesquioxide (Ge-132) (3a : R_1=R_2=R_3=H, X=OH) and related compounds having unique structures showed antitumor activity[3] and were capable of inducing of interferon[4].

The present paper discusses a simple synthesis, the structure, and reactivity of germatranes substituted with carboxyethyl groups. A comparison is made with Ge-132 related compounds with respect to physical and chemical properties and bioactivity.

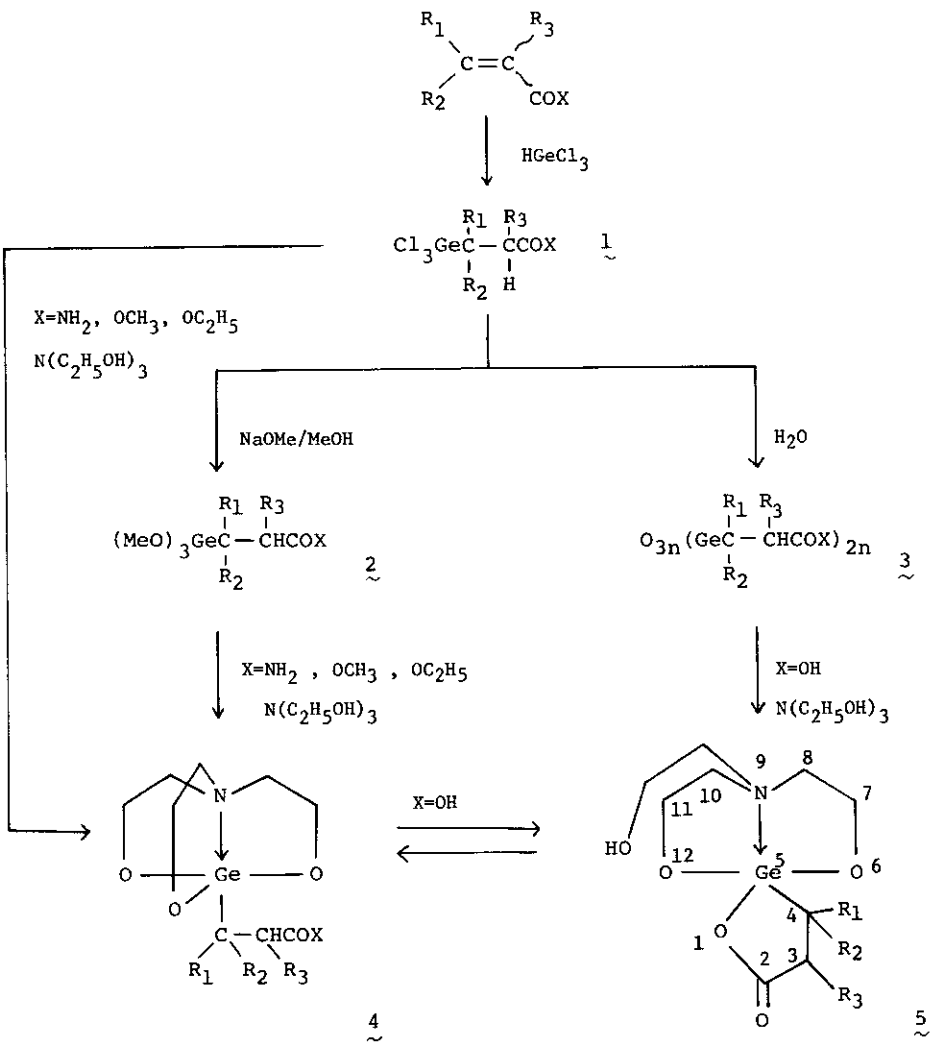


3 X=OH
X=NH_2



4 X=OH
X=NH_2

We previously reported a simple synthesis of 1-substituted germatranes via methanolysis of trichlorogermyl adducts 1 by sodium methoxide followed by refluxing with triethanolamine, and direct reaction of 1 with triethanolamine in the presence of sodium hydride[5]. However, we were unable to obtain the desired compounds (4a : R_1=R_2=R_3=H, X=OH) by such a method of synthesis. Thus, the reaction of the carboxyethylgermanium sesquioxide 3a, prepared by hydrolysis of the corresponding trichlorogermyl adduct 1a, with triethanolamine, was investigated. On refluxing in benzene with triethanolamine, carboxyethylgermanium sesquioxide 3a did not afford the desired product, carboxyethylgermatrane 4a, but the known spiro compound having a lactone ring system, 9-(2'-hydroxyethyl)-1,6,12-trioxa-9-aza-5-germaspiro[4,7]dodecan-2-one (5a : R_1=R_2=R_3=H)[6] was obtained in an 80% yield.



Scheme 1

The structure of 5a and the presence of the N→Ge interaction were previously established by the X-ray crystallographic analysis of Mironov et al[6]. However, the 90 MHz ^{1}H NHR spectrum of 5a showed many complex signals in a liquid state. The 400 MHz ^{1}H and 400 MHz ^{13}C NMR spectroscopic data confirmed the occurrence of the 1:1 tautomeric transformation of germocine 5a and germatrane 4a in a 5a solutions in DMSO-d_6 and DMF-d_6 (Fig. 1., Fig. 2., Table I). More recently, Mironov et al[7] also reported this unusual tautomeric rearrangement germocine⇄germatrane using 5a and its analogous spirocyclic germocines with a lactone ring from his 100 MHz NMR spectroscopic data.
A similar procedure was conducted to obtain 5b-f from sesquioxides 3b-f in good yields.

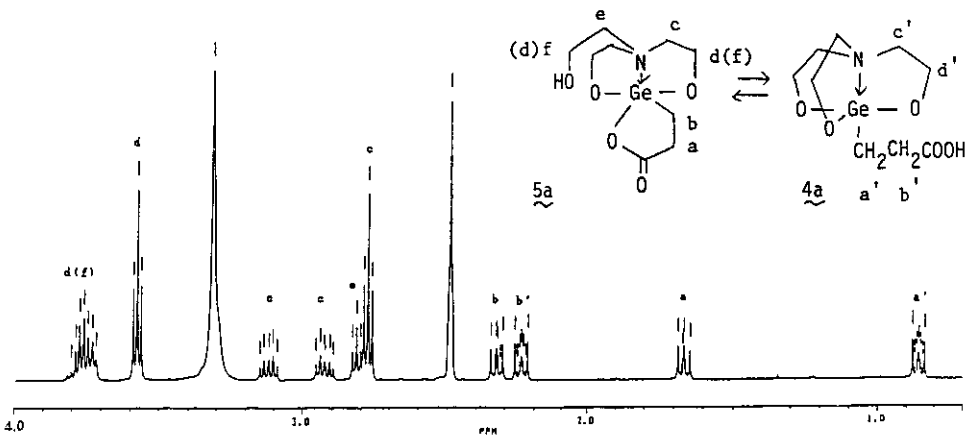


Fig. 1. 400 MHz ^{1}H-NMR Spectrum of the germocine 5a in DMSO-d_6 solution

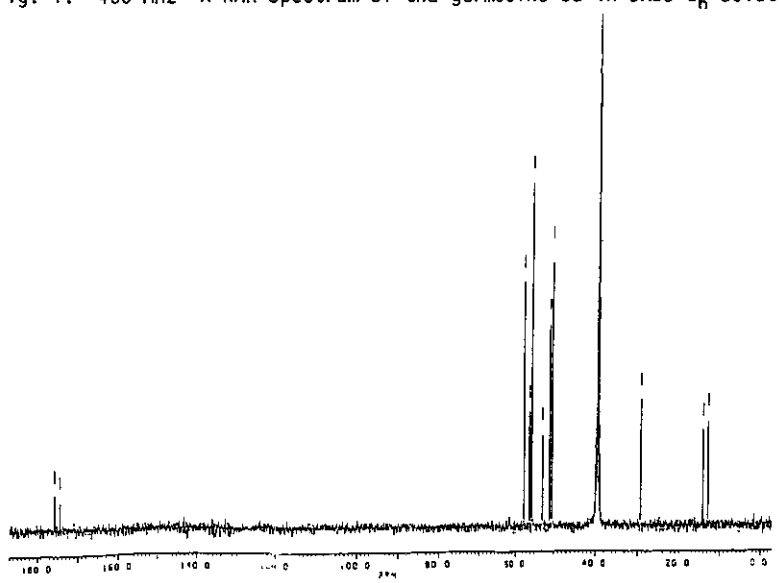
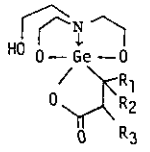


Fig. 2. ^{13}C-NMR Spectrum of the germocine 5a in DMSO-d_6 solution

Table I. Chemical shifts and coupling constants of 5a in DMSO-d_6

proton	chemical shift (δ ppm)	
	4a	5a
$GeCH_2$	0.87(m)	1.65(m)
$COCH_2$	2.23(m)	2.33(m)
NCH_2	2.78(t, J=6.0)	3.12(m)
NCH_2CH_2OH	-	2.92(t, J=6.5)
OCH_2	3.58(t, J=6.0)	3.74(m)
NCH_2CH_2OH	-	3.78(t, J=6.5)

Table II. The compounds 5, 9-(2'-hydroxyethyl)-1,6,12-trioxa-9-aza-5-germaspiro[4,7]dodecan-2-ones



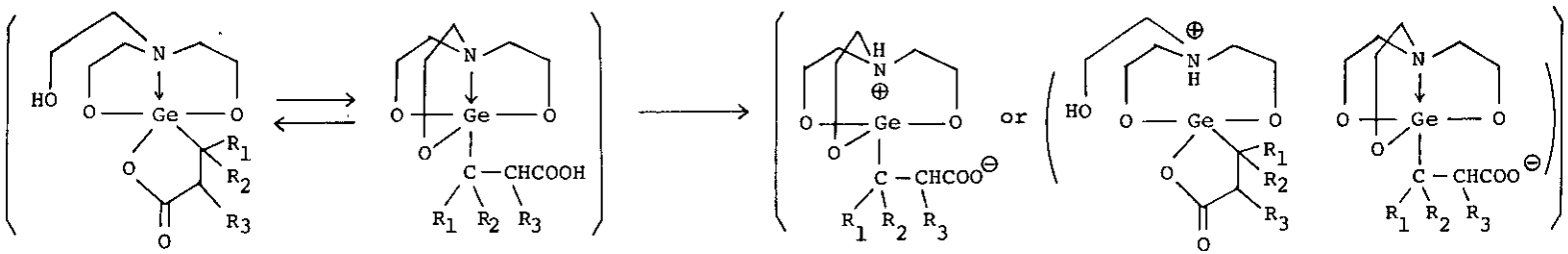
5	R_1	R_2	R_3	Yield (%)	MP (°C)	IR(cm^{-1}) C=O,	N → Ge	GeO	Molecular formula[a]	MS m/z
a	H	H	H	80,(92)[b]	184	1670	570,540	900,910 920	$C_9H_{17}GeNO_5$	293
b	CH_2	H	H	75	175	1680 1650	570,540	830,920	$C_{10}H_{19}GeNO_5$	307
c	H	H	CH_3	75,(85)[c]	168	1680	570,540	910,920	$C_{10}H_{19}GeNO_5$	307
d	CH_3	H	CH_3	77	195	1650	570,540	830,900 920	$C_{11}H_{21}GeNO_5$	319
e	CH_3	CH_3	H	65	119	1660 1630	570,520	860,920	$C_{11}H_{21}GeNO_5$	319
f	C_6H_5	H	H	42	180	1660	570,540	800,840 920	$C_{16}H_{23}GeNO_5$	369

a Elemental analyses of these compounds were within acceptable limits.

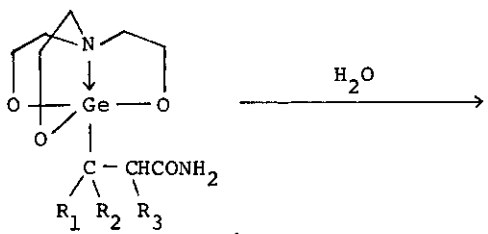
b Ref[6]

c Ref[7]

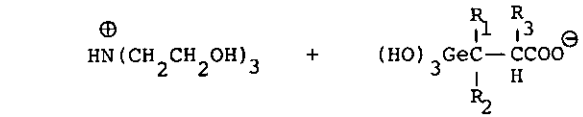
The results of the preparation of 5 are summarized in Table II. It should be noted that the IR spectra of 5 generally showed an absorption band corresponding to the carbonyl group of germa-γ-lactone at an unusually lower frequency (1630cm^{-1}-1680cm^{-1}), compared to that of the γ-lactone. On the hydrolysis of germocines 5a-f and the amide 4g, 5a-f were generally rapidly hydrolyzed to afford ion pairs of triethanolamine and trihydroxygermylpropanoic acid derivatives[8]. On the other hand, 4g was slowly hydrolyzed to give triethanolamine and trihydroxygermylpropanamide 8g[8]. Differences in relative rates of hydrolysis of germocine 5 and the amide 4g may be explained by the process in Scheme 2. Under such conditions that the equilibrium between the germocine 5 and germatrane 4 can be expected like in water as in DMSO, 4 may possibly be led to the zwitterionic intermediates 6 and 7 by proton transfer. These intermediates are easily attacked by water to produce ion pairs. In the case of amide 4g, the transannular N→Ge bond may be stable without such protonation on N, and therefore, an attack of water on the electronegative germanium atom is slower. An equilibrium between Ge-132 3a and trihydroxygermylpropanoic acid 8a in water was also observed by ESR and ^{13}C NMR spectroscopic data[9]. It thus appeared that Ge-132, the germocine 5a-f, and the germatrane (4a-f and 4g) may also afford similar key intermediates, trihydroxygermylpropanoic acid derivatives 8, in vivo. These intermediates seem to be important for their outset of biological activity.



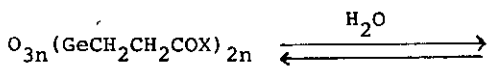
5a-f 4a-f 6 7



4g



8g



3a X=OH

3g X=NH_2

8a X=OH

8g X=NH_2

Scheme 2

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Received, 29th September, 1986