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SYNTHESIS OF GERMANIUM DERIVATIVES OF URACIL AND 5-FLUOROURACIL[¶]

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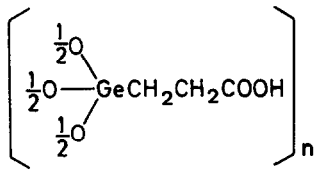
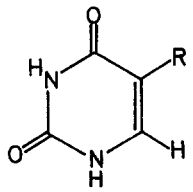
Abstract: N,N-Diacetate of uracil and 5-fluorouracil reacted with trichlorogermane to afford the Michael addition products, 1H,5H,6H-3-acetyl-6-trichlorogermylpyrimidine-2,4-dione and 1H,5H,6H-3-acetyl-5-fluoro-6-trichlorogermylpyrimidine-2,4-dione, respectively, which were hydrolyzed to the corresponding deacetylated germanium sesquioxides.

In recent years, some silicon- or germanium-containing organic compounds have attracted considerable attention because of their potential clinical application as anti-cancer drugs. Indeed we[1] and others[2] have previously reported the synthesis of the sesquioxide of β-germyl propionic acid(Ge-132) by the Michael addition of trichlorogermane to acrylic acid. The structure of Ge-132 has been confirmed by an X-ray analysis.[3] Its biological test has shown that Ge-132 not only possesses antitumor activities[4,5], but also functions as an inducer of interferon[6,7] with almost no detectable sign of toxicity.[8,9] Encouraged by these promising results, we developed the idea that the incorporation of a germanium residue into compounds of fundamental biological importance would enhance their anti-cancer activities to a significant degree, while their toxicity would be reduced at the same time. We wish to describe herein two representative examples, the germanium derivatives of uracil and 5-fluorouracil.



Ge-132

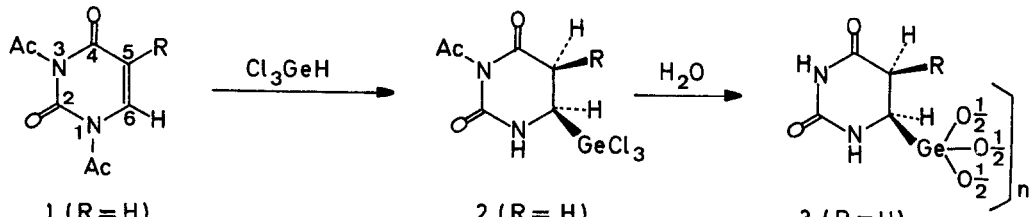


R = H, Uracil
R = F, 5-Fluorouracil(5-FU)

Uracil, 1H,3H-pyrimidine-2,4-dione, failed to give the desired Michael adducts upon treatment with trichlorogermane in ether or in chloroform probably because of the keto-enol tautomerism which tends to reduce the reactivity of the double bond toward the nucleophile. In order to suppress the tautomerism, the mobile protons on the nitrogens were first removed by acetylation. This was achieved by the treatment of uracil with acetyl chloride in dioxane in the presence of triethylamine at room temperature(Schotten-Baumann reaction[10]) to give the N,N-diacetate

[¶]A part of this work has been presented at 10th Symposium on Nucleic Acids Chemistry held in Kyoto, Japan, Nov., 1982.

(1) in 74% yield.[11] Compound 1 reacted with 2 moles of trichlorogermane in chloroform at room temperature for 24 h to give the trichlorogermyl adduct, 1H,5H,6H-3-acetyl-6-trichlorogermyl-pyrimidine-2,4-dione (2), in 60% yield.[12]



1 (R = H) 2 (R = H) 3 (R = H)

4 (R = F) 5 (R = F) 6 (R = F)

The structure of compound 2 was assigned by elemental analysis, NMR spectroscopy(^{13}C and ^{1}H) and IR.[12] The IR spectrum showed three carbonyl absorption bands at 1760, 1705 and 1605 cm^{-1}, corresponding to the two carbonyls in the ring and one acetyl on one of the nitrogens. The presence of a single acetyl group was clearly seen in the ^{1}H-NMR(δ2.70, s, 3H) as well as in ^{13}C-NMR spectra(δ176.39, s). The assignment of its location was based on the previous observation[10] that the N-1 acetyl is generally more susceptible to be removed than the N-3 acetyl. The assignment of H-5 and H-6 was made unambiguously by considering the electronegative property of the trichlorogermyl moiety and the splitting pattern characteristic of an ABC spin system. Although germanium itself is much less electronegative than carbon, trichlorogermyl moiety is electron-withdrawing due to the three electronegative chlorine atoms attached to it. This was further confirmed by ^{13}C-NMR spectrum which showed a triplet at δ 33.10(C-5) and a doublet at δ 49.19(C-6) besides two ring carbonyls (δ149.74, 168.86, each as a singlet)[3] and two other peaks due to the N-3 acetyl. The ^{1}H and ^{13}C-NMR data are summerized in Tables 1 and 2, respectively. The two IR bands due to Ge-C(600 cm^{-1}) and Ge-Cl(400 cm^{-1}) also supported this structure.[4]

When the germanium adduct 2 was stirred at 60°C with a large excess of water for 2 h, deacetylation and hydrolysis of the trichlorogermyl group took place to afford the germanium sesquioxide 3, 1H,3H,5H,6H-6-sesquioxidogermylpyrimidine-2,4-dione, in 81% yield.[5] The structure of this compound was confirmed by its NMR(^{13}C and ^{1}H) and IR spectral data.[5] Replacement of the three chlorine atoms by more electronegative oxygen atoms caused significant upfield shift of both proton and carbon at position 6; Δδ(H-6)=0.59, and Δδ(C-6)=7.35. This is in accord with our previous observations.[16] Replacement of chrorine by oxygen also caused a substantial change in ^{3}J values which must be ascribed to a structural change of the uracil ring. A detailed study of this process will be described elsewhere. It must be added that in D_2O solution the sesquioxide 3(and 6) are dissociated into its monomeric form. In DMSO-d_6, the same compound exhibits very broad ^{13}C peaks characteristic of the polymeric sesquioxides.

Subsequently, the same reaction sequence as described above was pursued using 5-fluorouracil(5-FU) for which we might expect enhanced biological activities because of the fluorine atom located at C-5. The diacetate(4)[7] of 5-FU obtained by the above procedure in 91% yield[10] was allowed to react with 3 moles of trichlorogermane in ether to afford the monoacetate of the Michael adduct 1H,5H,6H-3-acetyl-5-fluoro-6-trichlorogermylpyrimidine-2,4-dione

Table 1. ^{1}H-NMR data of uracils (1-3) and fluorouracils (4-6)

^{1}H	δ					J(Hz)			
	H-1	Ac-1	Ac-3	H-5	H-6	H-5 H-5	H-5 H-6	F-5 H-5	F-5 H-6
1[a]	-	2.51	2.67	5.86	8.14	-	8.0	-	-
2[a]	10.3	-	2.70	2.90, 3.15	4.55	16.8	12.3, 4.8	-	-
3[b]	-	-	-	2.83, 3.14	3.96	17.1	7.2, 5.4	-	-
4[b]	-	2.58	2.70	-	8.35	-	-	-	7.0
5[a]	8.0	-	2.81	5.69	4.77	-	2.0	45.0	42.9
6[b]	-	-	-	5.68	4.39	-	8.0	46.0	9.0

[a] In acetone-d_6. [b] In D_2O.

Table 2. ^{13}C-NMR data of uracils (2-3) and fluorouracils (5-6)

^{13}C	δ						J(Hz)		
	CO-2	CH_3-3	CO-3	CO-4	C-5	C-6	F-5 C-4	F-5 C-5	F-5 C-6
2[a]	149.74	23.46	176.39	168.86	33.10	49.19	-	-	-
3[b]	155.27	-	-	172.66	31.27	41.84	-	-	-
5[a]	148.28	23.62	177.53	163.34	84.87	54.21	22.0	181.9	25.6
6[b]	150.88	-	-	165.44	79.94	43.24	19.5	179.5	34.2
6[c]	151.97	-	-	165.21	82.92	47.36	23.2	182.2	29.3

[a] In acetone-d_6. [b] In D_2O. [c] In dimethylsulfoxide-d_6.

(5) in 78% yield.[18] Elemental analysis and spectral data(NMR and IR) strongly suggested that the reaction occurred in completely stereoselective manner to give a single adduct exclusively. In its ^{1}H-NMR spectrum, the ^{1}H-^{19}F couplings were evident; $^{2}J_{HF}$ = 45.0 Hz and $^{3}J_{HF}$ = 42.9 Hz.[19] A large magnitude of $^{3}J_{HF}$ is indicative of the antiperiplanar relationship between F-5 and H-6.[20] The two vicinal protons(H-5 and H-6) would then be in the gauche orientation, which may explain a small coupling between these protons($^{3}J_{HH}$ = 2.0 Hz). Hence the addition of trichlorogermane to 5-FU took place stereoselectively in a trans fashion. The high stereoselectivity can be explained by an attractive interaction between electronegative fluorine atom and much less electronegative germanium atom in the transition state of the Michael addition.

Compound 5 was similarly hydrolyzed with 18% hydrochloric acid at room temperature for 2 d to give the deacetylated germanium sesquioxide (6), 1H,3H,5H,6H-5-fluoro-6-sesquioxidegermylpyrimidine-2,4-dione, in 62 % yield.[21] Here again, a considerable change in chemical shifts

of H-6 and C-6 as well as in interproton and proton-fluorin coupling constants took place upon replacement of chlorine by oxygen.

Studies on biological activities of the germanium compounds described herein are now in progress and will be reported in due course.

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11) mp 58-59°C. IR(KBr) 1780, 1735, 1680, 1630, 1575 cm^{-1}. MS m/e 196(M^+), 43(base peak, CH_3CO).

12) mp 152-154°C. IR(KBr) 1760, 1705, 1605, 600, 400 cm^{-1}. Anal. Found: C, 21.86; H, 2.42; N, 8.22; Cl, 30.75; Ge, 21.39%. Calcd. for $C_6H_7O_3N_2GeCl_3$: C, 21.57; H, 2.12; N, 8.39; Cl, 31.83; Ge, 21.73%. (A small descrepancy observed in the analytical and calculated values of chlorine and germanium content is due to hygroscopic nature of the compound.)

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15) IR(KBr) 3250, 1700, 900, 820, 600, 400 cm^{-1}.

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17) mp 92-94°C. IR(KBr) 1790, 1740, 1725, 1680, 1080 cm^{-1}.

18) mp 198-200°C. IR(KBr) 1725, 1720, 1625, 1100,600, 385 cm^{-1}. Anal. Found: C, 20.28; H, 1.77; N, 7.71; Cl, 30.15%. Calcd. for $C_6H_6O_3N_2GeCl_3F$: C, 20.47; H, 1.72; N, 7.96; Cl, 30.21%.

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21) IR(KBr) 3300, 1705, 880, 590, 400 cm^{-1}.

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