Spirans XXII. Synthesis of 4,4-Dialkyl-4-germacyclohexanone and 8,8-Dialkyl-8-germaazaspiro [4.5] decanes

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4,4-Dialkyl-4-germacyclohexanones have been synthesized and their reactions studied. The diethyl ketone has been converted into *N*-(-dimethylaminopropyl)-2 aza-8,8-diethyl-8-germaspiro[4.5]decane (**16**). The biological properties of **16** have been examined in some detail. The reactions of this new ketone with some other reagents are reported.

As part of a continuing study of azaspirans, containing a spiro carbon atom, we have prepared azaspirans with a variety of elements replacing carbon in the A ring of the azaspiran moiety. In our studies, both the dialkylaminoalkyl substituent and the Z portion of the azaspiran have

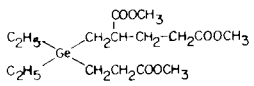
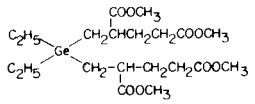
Z O, S, N-R, $Si(CH_3)_2$, CR_2
R dimethylaminopropyl

been extensively permuted. It has been shown that where Z is carbon the replacement of the hydrogens on Z leads to greater cytoxic activity than in the case of unsubstituted compounds. This appeared to be best where the substituent on Z is represented by *t*-butyl, trifuoromethyl or a polymethylene chain which is part of an additional ring. The compounds of oxygen, sulfur and nitrogen for Z all had decreased activity. (1) Therefore, it was gratifying when we prepared the isosteric compound in which Z was dimethylsilicon (2) or the *t*-butyl substituent was replaced by trimethylsilyl (3) and found that these groups also gave enhanced activity with good physiological compatability. As the dimethylsilicon derivative contributed a different electronegativity to the molecule and tended toward a more metallic derivative, we decided that the next higher isoster, as one goes down the group IVb elements in the periodic table, would be of interest. Perhaps it is better to relate this to the polarizability of the elements rather than electronegativity in going from carbon to germanium (4a). In addition the d orbital of germanium may lead to the ability to accept electrons or charge transfer for formation of co-ordination compounds.

Germanium is a very common element but is always present in very limited amounts. Organogermanium compounds have been studied much less than silicon and only after 1922 did they receive broader attention. Its biological activity and toxicity have only a limited literature (4b).

As the intermediate 4,4-diethyl-4-germacyclohexanone (**11**) was desired, our attention was directed to the preparation of the diester (**6**) (5) directly from diethylgermanium dihydride (**1**), which was easily obtainable by reduction of diethylgermanium dichloride. The reaction sequence is shown in Scheme I. Although we worked extensively with the dimethyl compounds, the bulk of our effort was concentrated on the diethyl compounds because of the greater ease of handling and the initial better yields.

Diethylgermanium dihydride was treated with methyl acrylate in a bomb tube at 100° and the mixture was distilled. The monoester (**4**), and diester (**6**) and a higher boiling fraction were generally formed in the ratio of 1:1:1.5, respectively. The monoester (**4**) could be converted easily, in a somewhat better yield, to diester (**6**), by recycling with methyl acrylate. The high boiling fraction and residues were collected from various runs and distilled (b.p. 120-225° at 0.04 mm). Successive fractions could be isolated which indicated the addition of one, two or more moles of methyl acrylate to the diester (**6**) as

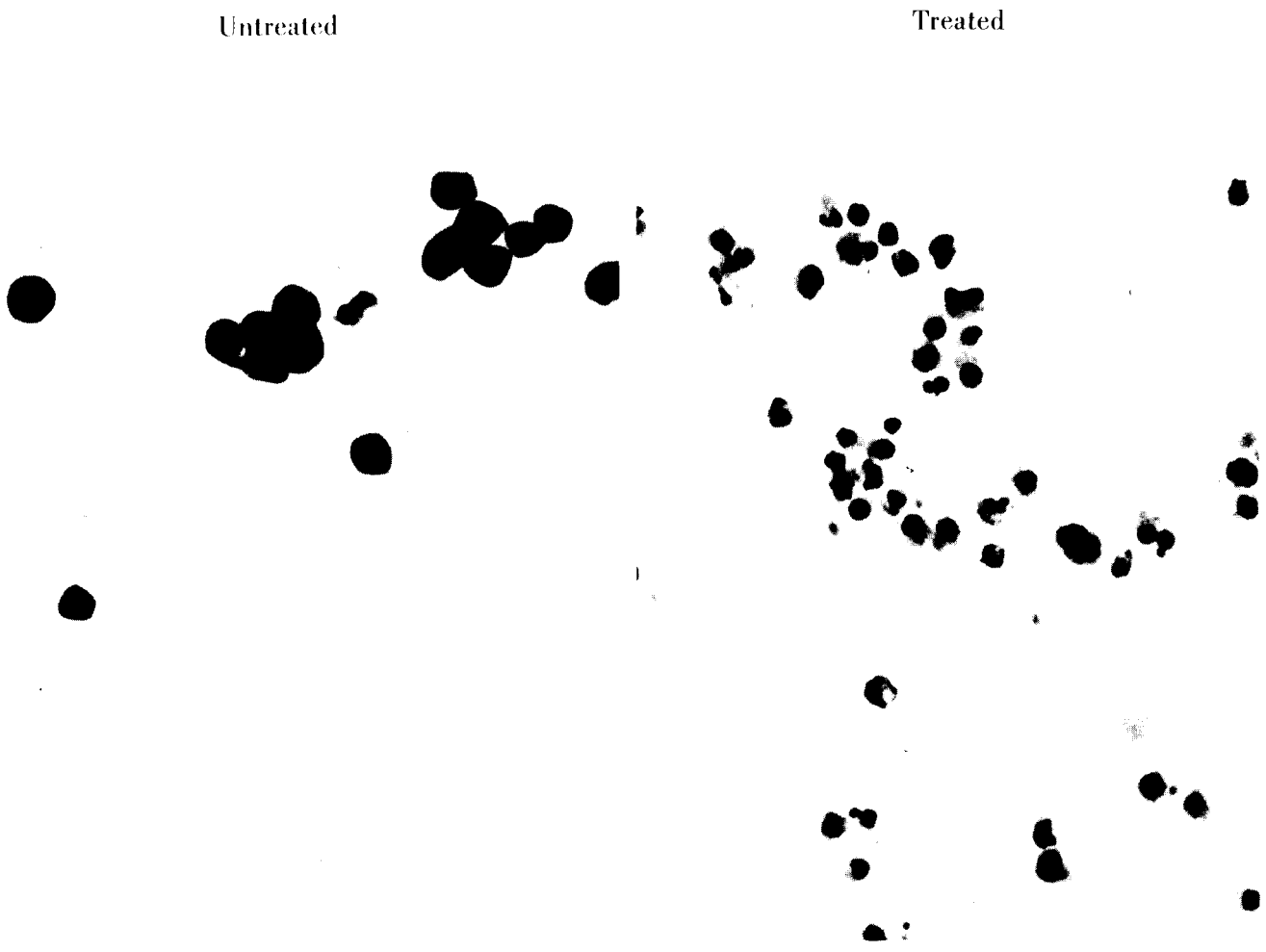



indicated. This was indicated by an increase in carbon content with a decrease in germanium percent of each higher boiling fraction. Supporting evidence for these structures was obtained from an nmr spectrum of the distillate and combined gas chromatography mass spectrometry. This showed clearly molecules containing 3,4,5 and 6 moles of acrylate in addition to the desired product.

The corresponding mono and dicarboxylic acids were obtained by saponification of the appropriate esters (**3**, **4**, **5**, **6**). The diacids were solids, whereas, the mono acids were oils. In the attempted purification of diethyl(β-carboxyethyl)germane by distillation at 1.5 mm, a second substance formed and sublimed in the column as the temperature increased. From molecular weight, elemental analysis, ir and nmr spectra and titration studies, it was evident that this substance was formed by the splitting out of hydrogen from the carboxyl group and the Ge–H bond of (**4**), and was an internal lactone corresponding to compound (**7**).

The diesters (**5**, **6**), on cyclization with potassium *t*-butoxide in toluene under nitrogen, gave the corresponding keto esters (**8**, **9**) which gave strong blue enol test with alcoholic ferric chloride solution. These keto esters were hydrolyzed and decarboxylated by refluxing 20% sulfuric acid and yielded the ketones (**10**, **11**). The new cyclic germanium ketones proved to be stable to a variety of reagents in that they could be recovered unchanged after three hours of refluxing with 20% sulfuric acid, 20% hydrochloric acid and 10% potassium hydroxide and underwent the usual reactions used for the preparation of derivatives.

Fig. 1



Cultures of human lymphoma cells before and after treatment with Germanium azaspirane.

The diethyl germanium ketone (**11**) was reacted with ethyl cyanoacetate using the procedure of Cope (**6**) to give ethyl-α-cyano-α-(4,4-diethyl-4-germacyclohexylidene)acetate (**12**). Treatment with alcoholic potassium cyanide and hydrolysis of the dicyano compound with concentrated hydrochloric acid gave the diacid (13). It was found that a short hydrolysis period of three to four hours was the best as longer lengths of time produced some cleavage of the germanium carbon bond with the production of oily by-products, which made purification of the diacid difficult. Dehydration to the corresponding anhydride (**14**) by means of acetic anhydride was readily achieved in excellent yield.

The germaazaspirandione (**15**) was prepared by reaction of the anhydride (**14**) with dimethylaminopropylamine and heating at 180° until water ceased to be evolved. Reduction of the dione by means of lithium aluminum hydride readily afforded the base (**16**) which was converted to its dihydrochloride and dimethonium salts.

With a considerable amount of ketone (**11**) available, it was of interest to study some other reactions which would compare the reactivity of this ketone with other ketones. One of these reactions was the Guareschi reaction (7) which proved unsuccessful.

The ketone readily gave the Wittig ester (**17**) by reaction with triethylphosphonoacetate in the presence of sodium hydride (8). The Wittig ester was hydrolyzed smoothly with alcoholic potassium hydroxide to the acid (**18**), which was obtained as a high boiling oil. Conversion of the acid to the unsaturated methyl ketone (**19**) by means of methyl lithium in ether was clean and proceeded without difficulty (9). Reaction of anhydride (**14**) with ethanol yielded a half ester and this ester was converted by means of the Arndt-Eistert reaction to the diacetic acid successfully but in poor yield.

The biological study of the germanium containing azaspiran (**16**) was examined as the dihydrochloride in some detail. It had an LD_{50} of 75 mg./kg. intraperitoneally in rats. The acute intraperitoneal and oral LD_{50}'s in the mouse were 150 and 324 mg./kg. respectively. The compound had no effect on the CNS profile up to 12 mg./kg. i.p. in the mouse. No toxic effects were reported when chronic toxicity studies in rats were carried out at a daily dosage level of 5 mg./kg. for a period of six months.

The compound was screened in tissue cultures with the potency depending on the system of cells used. For example, with P-388, L-1210 and KB cells, the values were 0.02, 0.2 and 0.3 μg. per ml. needed for cytolysis.

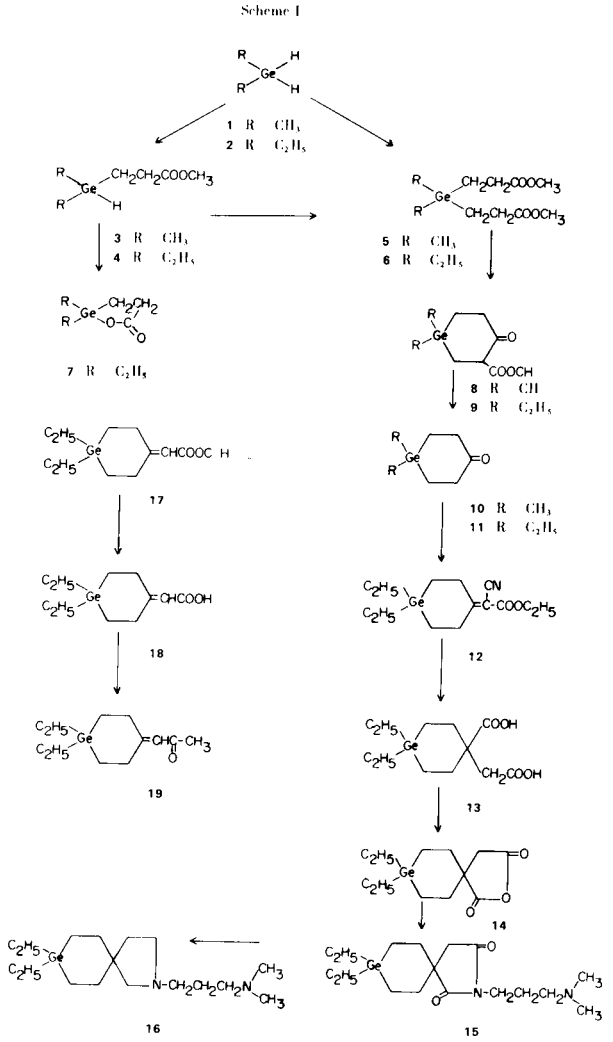
In cultures of human lymphoma cells the compound in the media at a concentration of one μg. per ml. on three successive exposures with an intervening interval of drug-free media for 48 hours, showed atrophy and degeneration of 95% of the cells. Most of the nuclei were fragmented (Fig. 1).

The mode of action in producing cytolysis appeared to be through the inhibition of protein synthesis (as the DNA and RNA synthesis were not initally altered) as measured by radioactive amino acid uptake. Protein synthesis was depressed by 66% in these tests. Various cases of advanced carcinoma have been treated for up to three years with gratifying results. None of the intermediate compounds showed any activity in tissue culture studies.

In the screening in the mouse against such systems as L-1210, B-16 and P-388 little activity was noted. This might be attributed to the binding of the compound to some constituent of the mouse serum. The compound inhibited the growth of Walker 256 in the rat by approximately 50% at a dosage of 50 mg./kg.

The dimethiodide of compound (**16**) in the anesthetized dog required only 0.13 mg./kg. i.v. to lower the mean arterial blood pressure by 30 mm Hg. This effect was by ganglionic blockage. Mercamylamine for comparison in the same test required 0.8 mg./kg.

Scheme I



EXPERIMENTAL

All melting points (Thomas Hoover capillary-type) are uncorrected. Nmr spectra were obtained on a Varian 60-Mc spectrometer using tetramethylsilane as internal reference. The ir spectra of all compounds corresponded with the assigned structures. Elemental microanalysis were performed by Schwarzhopf Microanalytical Laboratory, Woodside, New York. The intermediate germanium compounds were obtained from T. N. O., Institute for Organic Chemistry, Utrecht, The Netherlands.

Mass spectra were obtained on an LKB-9000 combined gas chromatograph-mass spectrometer. We thank Dr. H. M. Fales of the National Heart and Lung Institute for access to this machine. Germanium compounds exhibit characteristic multiplets of four peaks each separated by two mass units. As the lower three of these are of approximately equal intensity, the mass spectra are reported on the basis of the middle peak of each multiplet.

Diethyldi-(β-carbomethoxyethyl)germane (**6**).

A mixture 42 g. (0.316 mole) of diethylgermanium dihydride (**2**), and 55.1 g. (0.632 mole) of methyl acrylate were mixed and heated in a steel cylinder (Parr) for five hours. After cooling overnight, the mixture was heated at 20 mm using a rotary evaporator. The residue was distilled under reduced pressure and gave the following fractions:

1. 13.5 g., 34-38°, 0.04 mm
2. 13.2 g., 84-122°, 0.03 mm
3. 21 g., 128-184°, 0.03

Fraction 2 on redistillation gave the title compound, b.p. 80-82° (0.035 mm) 11 g.

Anal. Calcd. for $C_{12}H_{24}O_4Ge$: C, 47.27; H, 7.93; Ge, 23.81. Found: C, 47.38; H, 8.01; Ge, 23.99. Calcd. Mol. Wt.: 304.9. Found: 302.

Diethyl-(β-carbomethyoxyethyl)germane (**4**).

Fraction 1 (b.p. 34-38° at 0.04 mm) from the proceeding preparation was redistilled and yielded the title compound, b.p. 67-69° (3.0 mm) 10.1 g.

Anal. Calcd. for $C_8H_{18}O_2Ge$: C, 43.91; H, 8.29; Ge, 33.18. Found: C, 43.59; H, 8.22; Ge, 33.17. Mol. Wt. Calcd: 218.8. Found: 221.

Dimethyldi-(β-carbomethoxyethyl)germane (**5**).

The procedure of the above diethyl compound was followed employing 48.3 g. of dimethylgermanium dihydride (**1**), and of methyl acrylate. Because of the low boiling point of the dimethylgermanium hydride, the bomb was charged at 0°. The yield of crude esters was 67 g. which on distillation yielded only 4.8 of the pure title compound, b.p. 80-81° (0.21 mm).

Anal. Calcd. for $C_{10}H_{20}O_4Ge$: C, 43.38; H, 7.28; Ge, 26.22. Found: C, 43.30; H, 6.98; Ge, 26.13.

Dimethyl(β-carbomethoxyethyl)germane (**3**).

The preparation was carried out in the same manner as the above diester compound. From the amounts used only 2 g. of the desired ester was isolated, b.p. 72-75° (34 mm).

Anal. Calcd. for $C_6H_{14}O_2Ge$: C, 37.78; H, 7.40; Ge, 38.05. Found: C, 37.57; H, 7.22; Ge, 38.30.

Diethyldi(β-carboxyethyl)germane.

A solution of 3 g. of the diester, (**6**), and 50 ml. of 10% alcoholic potassium hydroxide was allowed to stand 24 hours at room temperature. The clear solution was evaporated under vacuum and the residue was dissolved in 100 ml. of water, filtered and acidified with hydrochloric acid. The precipitated oil crystallized on refrigeration overnight, m.p. 51.5-53.5°. 2.4 g. Recrystallization from ethyl acetate and then benzene petroleum ether gave material m.p. 52.5-53.5°.

Anal. Calcd. for $C_{10}H_{20}O_4Ge$: C, 43.35; H, 7.28; Ge, 26.22. Found: C, 43.64; H, 7.25; Ge, 26.60. Mol. Wt. Calcd: 277. Found: 280.

Diethyl(β-carboxyethyl)germane.

The monoester, (**4**), (5 g.) was hydrolyzed as above for the diester. After precipitation, the oil could not be induced to crystallize. The acid was extracted with ether, dried, and the ether evaporated. The residue (4 g.) was distilled b.p. 97-105° (1.5 mm) and this fraction was the pure acid (1 g.).

Anal. Calcd. for $C_7H_{16}O_2Ge$: C, 41.05; H, 7,88; Ge, 35.44. Found: C, 40.83; H, 7,78; Ge, 35.33. Mol. Wt. Calcd: 204.8. Found: 205.5.

Diethyl(β-carboxyethyl)germane Lactone (**7**).

In the above distillation of the mono acid a white substance formed and condensed in the column as the pot temperature increased above 150°. This material which boiled at 140-150° (1.5 mm), 2 g. melted at 128-133°. Recrystallization from ethyl acetate gave 1.5 g. of pure lactone, m.p. 134-135°; pmr: δ 1.3, less complex m, 10 H; 1.5, t, 2 H J = 6.7 Hz; 2.85, t, 2H, J = 6.7 Hz.

Anal. Calcd. for $C_7H_{14}O_2Ge$: C, 41.46; H, 6.96; Ge, 35.80. Found: C, 41.54; H, 6.86; Ge, 35.66. Mol. Wt. Calcd: 202.7. Found: 203.5.

Dimethyldi(β-carboxyethyl)germane.

The diacid was prepared from **5** as above using the procedure for the diethyl compound, m.p. 89-90° (ethyl acetate).

Anal. Calcd. for $C_8H_{16}O_4Ge$: C, 38.66; H, 6.43; Ge, 29.18. Found: C, 38.54; H, 6.37; Ge, 29.07. Mol. Wt. Calcd.: 248.8. Found: 250.

Dimethyl(β-carboxyethyl)germane.

The mono acid was prepared from **3** as above for the diethyl compound, but without distillation. It was an almost colorless oil.

Anal. Calcd. for $C_5H_{12}O_2Ge$: C, 33.96; H, 6.84; Ge, 41.07. Found: C, 34.15; H, 7.02; Ge, 40.75.

Preparation of Diethyldi(β-carbomethoxyethyl)germane (**6**) from Diethyl(β-carbomethoxyethyl)germane (**4**).

A mixture of 25 g. of diethyl(β-carbomethoxyethyl)germane (**4**) and 10 g. of ethyl acrylate were heated in a steel cylinder at at 100° for 5 hours. After cooling, the mixture was distilled and gave three fractions as follows: 8.3 g. of monoester 30-84° (0.04 mm) 13.5 g. of diester 85-105° (0.04 mm) and 10.8 g. of high boiling material 120-200° (0.04 mm) and 2 g. of residue (higher boiling). Redistillation of the middle fraction gave pure diester b.p. 87-91° (0.09 mm).

Higher Molecular Weight Fractions.

Fraction 3 from the above diethyl di(β-carbomethoxyethyl)-germane preparation and the preparation from the dihydride when subjected to fractional distillation gave fractions which corresponded to the addition of 1 mole of ethyl acrylate, b.p. 136-138° (0.02 mm) 31 g. and 2 moles of ethyl acrylate, b.p. 167-183° (0.03 mm) 3.0 g. to the diethyldi(β-carbomethoxyethyl)germane (**6**); pmr: δ 1.2, m; 2.2-2.9, m.3.9, s which represents 32% of total integral. The compond with two moles of acrylate requires 25% CH_3O.

Mass spectra (1% OV-17 column temperature programmed at 8°/minute from 90°) moles acrylate/mole diethyl germanium

dihydride.

(Two moles) 150°-m/e no parent ion at 304, large peaks at 275 (m - 29), 243, 217, 103 and 55 (no Ge).

(Three moles) 185°-m/e no parent ion at 390, large peaks at 361 (m - 29), 303, 217, 103 and 55 (no Ge).

(Four moles) 235°-m/e no parent ion at 476, large peaks at 447 (m - 29), 303, 161, 103 and 55 (no Ge).

(Five moles) 260°-m/e no parent ion at 562, large peaks at 533 (m-29), 389, 303, 161, 103, and 55 (no Ge).

Fraction b.p. 136-138° (0.02 mm).

Anal. Calcd. for $C_{16}H_{30}O_6Ge$: C, 49.16; H, 7.73; Ge, 18.56. Found: C, 59.55; H, 7.89; Ge, 20.0. Mol. Wt. Calcd.: 391. Found: 403.

Fraction b.p. 167-183° (0.03 mm).

Anal. Calcd. for $C_{20}H_{36}O_8Ge$: C, 50.35; H, 7.61; Ge, 15.22. Found: 51.0; H, 7.85; Ge, 16.2. Mol. Wt. Calcd: 477. Found: 465.

2-Carbomethoxy-4,4-diethyl-4-germacyclohexanone (**9**).

A solution of 23.9 g. (0.17 mole + 25% excess) of potassium *t*-butoxide in 1000 ml. of dry toluene was prepared in a 2 l. flask. While a stream of nitrogen was passed over the solution, it was brought to reflux. With stirring 51.8 g. (0.17 mole) of diethyldi-(carbomethoxyethyl)germane (**6**) was added dropwise over 45 minutes and the mixture was refluxed for 2 hours. The yellow solution turned to a brownish pink color and was allowed to cool overnight with stirring. The clear mixture was neutralized with 5% hydrochloric acid and washed twice with water. After drying the solution over sodium sulfate, the toluene was distilled off. Vacuum distillation of residue gave 32.5 g. (70%) of the keto ester b.p. 93-94° (0.42 mm). The product gave a strong blue positive enol test with alcoholic ferric chloride.

Anal. Calcd. for $C_{11}H_{20}O_3Ge$: C, 48.41; H, 7.38; Ge, 26.01. Found: C, 48.55; H, 7.62; Ge, 25.87.

2-Carbomethoxy-4,4-dimethyl-4-germacyclohexanone (**8**).

This was prepared in the same manner as the above diethyl compound, b.p. 65-68° (0.42 mm). From 4.2 of diester, (**5**), was obtained 1.2 g. of keto ester.

Anal. Calcd. for $C_9H_{16}O_3Ge$: C, 44.15; H, 6.59; Ge, 29.65. Found: C, 43.83; H, 6.42; Ge, 30.01.

4,4-Diethyl-4-germacyclohexanone (**11**).

To 23 g. of 2-carbomethoxy-4,4-diethyl-4-germacyclohexanone (**9**), in a 300 ml. flask, fitted with a magnetic stirrer, was added 150 ml. of 20% sulfuric acid. The mixture was refluxed with stirring for 8 hours and allowed to cool. After diluting with an equal volume of water, the ketone was extracted three times with 100 ml. portions of ether. The ethereal solution was washed twice with water, once with a saturated sodium bicarbonate solution, and again with water. The solution was dried over sodium sulfate and the ether removed under reduced pressure using a rotary evaporator. On distillation, the residue gave 12 g. (68%) of the product, b.p. 84-85° (1.5 mm), 108-110 (7.4 mm), pmr δ 1.1, complex m, 14 H; 2.7 t, 4 H, J = 5 Hz. Mass spectrum: m/e 214, 185 (m-29), 157, 101.

Anal. Calcd. for $C_9H_{18}OGe$: C, 50.31; H, 8.44; Ge, 33.79. Found: C, 50.12; H, 8.46; Ge, 33.61.

The semicarbazone was prepared in the usual manner, m.p. 195-196°.

Anal. Calcd. for $C_{10}H_{21}N_3OGe$: C, 44.45; H, 7.79; N, 15.46. Found: C, 44.31; H, 7.60; N, 15.70.

The 2,4-dinitrophenylhydrazone was prepared in the usual way, m.p. 136-136.5°.

Anal. Calcd. for $C_{15}H_{22}N_4O_4Ge$: C, 45.62; H, 5.61; N, 14.19. Found: C, 45.85; H, 5.53; N, 14.21.

4,4-Dimethyl-4-germacyclohexanone (**10**).

The title compound was prepared as described above for the diethyl compound. From 5 g. of the keto ester only 1.5 g. of the ketone was obtained, b.p. 86-90° (7.0 mm).

Anal. Calcd. for $C_7H_{14}OGe$: C, 45.00; H, 7.56; Ge, 38.87. Found: C, 45.14; H, 7.62; Ge, 38.62.

The semicarbazone was obtained in the usual manner, m.p. 190-192°.

Anal. Calcd. for $C_8H_{17}N_3OGe$: C, 39.41; H, 7.03; N, 17.23. Found: C, 39.12; H, 6.96; N, 16.93.

Ethylα-cyano-α-(4,4-diethyl-4-germacyclohexylidene)acetate (**12**).

A mixture 19.2 g. (0.08 mole) of 4,4-diethyl-4-germacyclohexanone, (**11**), 9.0 g. (0.08 mole) of ethyl cyanoacetate, 0.92 g. ammonium acetate, 0.95 g. of acetic acid and 100 ml. of benzene was refluxed with a Dean Stark water separator. When no more water was collected, the mixture was cooled and washed with three 40 ml. portions of water. The water washings were again washed with benzene and the combined benzene solutions were dried over sodium sulfate. After removal of the benzene by distillation, the residue was distilled to give 20.6 g. of oil, b.p. 126-127°(0.3 mm), 113-118° (0.05 mm) 77%.

Anal. Calcd. for $C_{14}H_{23}NO_2Ge$: C, 54.16; H, 7.48; N, 4.52; Ge, 23.42. Found: C, 54.01; H, 7.51; N, 4.62; Ge, 23.62.

4,4-Diethyl-4-germacyclohexane-1-carboxy-1-acetic Acid (**13**).

A solution of 20.6 g. of potassium cyanide dissolved in 60 ml. of water was added to a solution of 20.6 g. of ethyl-α-cyano-α-(4,4-diethyl-4-germacyclohexylidene)acetate (**12**) dissolved in 160 ml. of absolute alcohol. After standing at room temperature for 24 hours, the solvent was removed using a rotary evaporator under reduced pressure, and the residue was refluxed with 200 ml. of hydrochloric acid for 3-4 hours. The mixture was then diluted with 200 ml. of water and extracted with ether. The ether was removed and the residue was dissolved in sodium bicarbonate solution, filtered and precipitated with dilute hydrochloric acid. The oily acid was refrigerated and when solid, washed by decantation. The crude product was filtered, washed with water and dried, 10.2 g. Upon recrystallization from ethyl acetate, petroleum ether and then isooctane, the product melted at 111-112°. In some cases, the crude product after the 4-5 hour reflux could be filtered directly, was not oily, and could be recrystallized directly.

Anal. Calcd. for $C_{12}H_{22}O_4Ge$: C, 47.58; H, 7.32; Ge, 23.97. Found: C, 47.88; H, 7.20; Ge, 23.95.

4,4-Diethyl-4-germacyclohexane-1-carboxy-1-acetic Acid Anhydride (**14**).

Fifteen g. of the above acid (**13**) was refluxed with 60 g. of acetic anhydride for one hour. After cooling, the excess of acetic anhydride was distilled off at 20 mm pressure. The residue on distillation boiled at 126-130° (0.2 mm) and solidified in the receiver, m.p. 58-59°.

Anal. Calcd. for $C_{12}H_{20}O_3Ge$: C, 50.59; H, 7.08; Ge, 25.48. Found: C, 50.54; H, 6.90; Ge, 25.19.

N-(3-Dimethylaminopropyl)-2-aza-8,8-diethyl-8-germaspiro[4.5]-decane-1,3-dione (**15**).

To 6.8 g. of the finely powdered anhydride, (**14**), above was added 2.4 g. of 3-dimethylaminopropylamine. The mixture was heated until a homogeneous melt was obtained and then heating was maintained at 180° until water ceased to be evolved. The

product was vacuum distilled, b.p. 158-160° (0.22 mm) 7.2 g., 144-147° (0.05).

Anal. Calcd. for $C_{17}H_{32}N_2O_2Ge$: C, 55.33; H, 8.74; N, 7.59; Ge, 19.67. Found: C, 55.10; H, 8.70; N, 7.52; Ge, 19.39.

N-(3-Dimethylaminopropyl)-2-aza-8,8-diethyl-8-germaspiro[4.5]-decane (**16**).

Into a 1 l. 3 necked flask fitted with a stirrer, dropping funnel and a reflux condenser, was placed 5 g. of lithium aluminum hydride and 500 ml. of anhydrous ether. After stirring for 2 hours, a solution of 7 g. of *N*-(3-dimethylaminopropyl)-8,8-diethyl-8-germa-2-azaspiro[4.5]decane-1,3-dione (**15**) dissolved in 100 ml. of a benzene ether solution was added over a period of 30 minutes. The reaction was stirred for 4 hours and then decomposed by the slow dropwise addition of 20 ml. of water. After stirring an additional hour, the inorganic solids were filtered off and the ethereal filtrate was dried over sodium sulfate. The solvent was removed and the residue was distilled, b.p. 106-109° (0.03 mm) 5.4 g.

Anal. Calcd. for $C_{17}H_{36}N_2Ge$: C, 59.86; H, 10.64; N, 8.21; Ge, 21.29. Found: C, 59.65; H, 10.72; N, 8.17; Ge, 21.10.

The dihydrochloride was prepared in the usual manner with alcoholic hydrogen chloride and ether, m.p. 287-288°, (put in bath at 284°).

Anal. Calcd. for $C_{17}H_{38}Cl_2N_2Ge$: C, 49.32; H, 9.25; Cl, 16.89; N, 6.76; Ge, 17.54. Found: C, 49.12; H, 9.35; Cl, 16.62; N, 6.84; Ge, 17.65.

The dimethiodide was prepared in the usual manner by refluxing the base with an excess of methyl iodide in alcohol, m.p. 279-280°, (put in a bath at 274°).

Anal. Calcd. for $C_{19}H_{42}I_2N_2Ge$: I, 40.61. Found: I, 40.40.

N-(3-Diethylamino-2 hydroxypropyl)-2-aza-8,8-diethyl-8-germaspiro[4.5]dicane-1,3-dione.

This was prepared in the same manner as the above dimethylaminopropyl analogue employing 3-diethylamino-2-hydroxypropylamine, b.p. 175-180° (0.045 mm).

Anal. Calcd. for $C_{19}H_{36}N_2O_3Ge$: C, 55.24; H, 8.77; N, 6.78; Ge, 17.57. Found: C, 55.41; H, 8.90; N, 7.01; Ge, 17.29.

N-(3-Diethylamino-2-hydroxypropyl)-2-aza-8,8-diethyl-8-germaspiro[4.5]decane.

This was prepared as the dimethylaminopropyl derivative above, b.p. 133-138° (0.04 mm).

Anal. Calcd. for $C_{19}H_{40}N_2OGe$: C, 59.25; H, 10.46; N, 7.27; Ge, 18.85. Found: C, 58.98; H, 10.32; N, 7.00; Ge, 19.01.

Dihydrochloride was prepared in the usual way, m.p. 194-196° (acetonitrile).

Anal. Calcd. for $C_{19}H_{42}Cl_2N_2OGe$: Cl, 17.67. Found: Cl, 17.54.

Ethyl-α-(4,4-diethyl-4-germacyclohexylidene) Acetate (**17**).

The procedure in Organic Synthesis (8) was followed using 32.2 g. (0.15 mole) of 4,4-diethyl-4-germacyclohexanone (**11**), 6.135 g. (0.15 mole) of sodium hydride (57% in mineral oil), 35.35 g. of triethylphosphonoacetate (0.15 mole + 5% excess) and 100 ml. of benzene. After 3/4 of the ketone was added, the mixture formed a gummy precipitate which made stirring difficult. The mixture was extracted four times with benzene and after decanting the benzene was dissolved in 500 ml. of water. The aqueous solution was extracted three times with 100 ml. of benzene and combined with the other benzene extracts. After washing several times with water, the benzene solution was dried over sodium sulfate. The benzene was evaporated and the residue distilled, b.p. 79-82° (0.1 mm) 29.5 g.

Anal. Calcd. for $C_{13}H_{24}O_2Ge$: C, 54.80; H, 8.49; Ge, 25.48. Found: C, 55.08; H, 8.71; Ge, 25.20.

4,4-Diethyl-4-germacyclohexylidene Acetic Acid (**18**).

To 30 g. of ethyl-α-(4,4-diethyl-4-germacyclohexylidene)-acetate, (**17**), dissolved in 100 ml. of alcohol was added 100 ml. of 20% alcoholic potassium hydroxide, allowed to stand 24 hours, and was refluxed one hour. The solvent was stripped off and the residue was dissolved in water, filtered, treated with charcoal, filtered and acidified with hydrochloric acid. After standing several days, the oil which could not be induced to crystallize was extracted with ether. The extract was dried over sodium sulfate and the ether removed. Distillation gave the product which could not be induced to crystallize, b.p. 100-103° (0.07 mm) 26 g., pmr: δ 1.0, m, 14 H; 2.4, m, 2 H; 3.0 brs, 2 H; 5.75, s, 1 H; 11.6, s, 1 H. Mass spectrum: m/e 256, 209, 183, 101.

Anal. Calcd. for $C_{11}H_{20}O_2Ge$: C, 51.43; H, 7.85; Ge, 28.26. Found: C, 51.66; H, 7.96; Ge, 28.02.

4,4-Diethyl-4-germacyclohexylidene Acetone (**19**).

To a solution of 25 g. (0.1 mole) of the above acid, (**18**), dissolved in 200 ml. of anhydrous ether maintained at 0° and blanketed with nitrogen, was added dropwise with vigrous stirring, over a period of 2.5 hours, a solution of 0.21 mole of methyl lithium in 220 ml. of ether. The reaction mixture was stirred overnight while allowing it to come to room temperature. The almost clear solution was added to 400 ml. of a cold solution of 10% ammonium chloride and then acidified with dilute hydrochloric acid. After separating the ethereal layer, the aqueous solution was extracted twice with ether and the combined ether solutions washed with water and dried over sodium sulfate. The ether was removed and the residue was distilled, b.p. 121-125° (3.7 mm) 20.5g.; pmr: δ 1.0, m, 14 H; 2.15, s, 3 H; 2.2, m, 2 H; 3.1, brs, 2 H; 5.8, t, and 6.0, s, 1 H. Mass spectrum: m/e 254, 225, 181, 101.

Anal. Calcd. for $C_{12}H_{22}OGe$: C, 56.54; H, 8.70; Ge, 28.48. Found: C, 56.85; H, 8.88; Ge, 28.19.

4,4-Diethyl-4-germacyclohexane-1,1-diacetic Acid.

A mixture of 4.2 g. (0.015 mole) of 4,4-diethyl-4-germacyclohexane-1-carboxy-1-acetic acid anhydride (**14**) and 25 ml. of absolute alcohol was treated with a solution of 0.41 g. of sodium (0.022 mole) dissolved in 25 ml. of alcohol. After refluxing for an hour, all of alcohol was removed and the residue dried at 100° under vacuum for an hour. The dried salt was suspended in 75 ml. of anhydrous ether, 5 ml. of oxalyl chloride was added and the mixture was refluxed for two hours. Sodium chloride was removed by filtration and the clear solution was evaporated under reduced pressure to remove all solvent and excess oxalyl chloride. The residue, dissolved in 50 ml. of anhydrous ether, was added to an excess of diazomethane dissolved in 200 ml. of anhydrous ether, and the mixture refrigerated overnight. Excess diazomethan and ether were removed under reduced pressure.

The crude diazo ketone was dissolved in 25 ml. of alcohol, warmed to 50°, treated with an alcoholic slurry of silver oxide (from 2 g. of silver nitrate) and refluxed for an hour. The solution was filtered, treated with charcoal, the solvent was removed and the residue (3.7 g.) was taken up in anhydrous ether. Removal of the ether and distillation gave a fraction b.p. 123-128° (0.15 mm) 1.8 g. This crude ester was dissolved in 50 ml. of 10%

alcoholic potassium hydroxide solution and allowed to stand overnight. After removal of the solvent, the residue was dissolved in in water, treated with charcoal and filtered. Treatment of the solution with dilute hydrochloric acid gave an oil which solidified on standing in the cold, 1.5 g., m.p. 70-100°. The solid was dissolved in 50 ml. of sodium bicarbonate solution, filtered and reprecipitated with hydrochloric acid. Fractional recrystallization from alcohol petroleum ether yielded material melting at 154-157°, 0.6 g. Recrystallization from benzene petroleum ether gave the pure acid m.p. 160-161°, 0.3 g.; pmr: δ 0.9, m, 14 H; 1.8, m, 4 H; 2.5 brs, 4 H; 11.5, s, 2 H. Mass spectrum (probe, 90°): m/e no parent ion, large peaks at 287 (m-C_2H_5), 269 (M-47), 183, 155, 101.

Anal. Calcd. for $C_{13}H_{24}O_4Ge$: C, 49.27; H, 7.64. Found: C, 48.41; H, 7.42.

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