anol, yield 48 g. or 81%, m. p. 69–70°, colorless rhombohedra. *Anal.* Calcd. for $C_8H_7O_3Cl_3S$: C, 33.16; H, 2.42; Cl, 36.79. Found: C, 33.53, 33.26; H, 2.78, 2.55; Cl, 36.68.

An attempt to prepare this compound by heating 3,4-dichlorobenzenesulfonyl chloride and excess ethylene chlorohydrin under reflux resulted in only poor yield of the ester.

Preparation of the *p*-Chlorobenzenesulfonamides.—To a stirred solution of *p*-chlorobenzenesulfonyl chloride (1 mole) in chloroform was added dropwise the amine (1 mole) (free amine or aq. solution) over a period about one-half hour. The reaction mixture was kept below 40° by cooling. Then an aqueous solution of sodium hydroxide (1 mole) was added dropwise with cooling and stirring. After stirring for an additional half-hour, the reaction mixture was allowed to separate. The organic layer was washed with water and the solvent removed. Yields of the white *p*-chlorobenzenesulfonamides were quantitative. They were crystallized from ethanol or petroleum ether.

N-(β-Chloroethyl) *p*-Chlorobenzenesulfonamide.—To N-(β-hydroxyethyl) *p*-chlorobenzenesulfonamide (5 g.) was added thionyl chloride (10 cc.) and the solution heated under reflux for two hours. The reaction mixture was stirred with water to decompose excess thionyl chloride and the precipitated white solid (3.0 g. 58%) was filtered, washed with water and dried. Crystallization from ethanol or ethyl acetate yielded white plates (2.0 g.), m. p. 152–153°. *Anal.* Calcd. for $C_8H_9O_2SNCl_2$: C, 37.80; H, 3.54; N, 5.51. Found: C, 36.80, 36.97; H, 3.25, 3.38; N, 5.35, 5.89.

The Action of Chlorine on *p*-Chlorobenzenesulfonyl Chloride.—*p*-Chlorobenzenesulfonyl chloride (50 g.) and a trace of ferric sulfate was heated in a flask equipped with a condenser and a gas inlet tube at 175–180° while a rapid stream of chlorine gas was passed in for one hour. The white solid (12.5 g.) which sublimed into the condenser melted at 52–54° and did not depress the melting point of *p*-dichlorobenzene. The material left in the pot on distillation yielded 10.5 g. more of *p*-dichlorobenzene, total yield 22.5 g. or 63%, b. p. 172–180° and a fraction (9 g.) b. p. (12 mm.) 125–130°; crystallized from ethanol, m. p. 50–52° (4 g.) (the melting point of 1,2,3,5-tetrachlorobenzene is 51°). The oily product left in the mother liquors is probably a mixture of the three isomeric tetrachlorobenzenes.

Summary

p-Chlorobenzenesulfonic acid was converted to *p*-chlorobenzenesulfonyl chloride and fluoride and from these several new sulfones, sulfonic esters and N-substituted sulfonamides were prepared.

The esterification of glycerol α-monochlorohydrin with *p*-chlorobenzenesulfonyl chloride resulted in 3-chloropropyl bis-1,2-(*p*-chlorobenzenesulfonate), 2-(1,3-dichloropropyl)-*p*-chlorobenzenesulfonate and 1,2,3-trichloropropane.

The reaction of chlorine with *p*-chlorobenzenesulfonyl chloride yielded *p*-dichlorobenzene.

GUELPH, ONTARIO, CANADA RECEIVED AUGUST 24, 1949

[CONTRIBUTION FROM THE MALLINCKRODT CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Dimethylgermanium Oxide. Toxicity and Effect on Blood Composition

BY EUGENE G. ROCHOW AND BERNICE M. SINDLER

Early work on the biological effects of germanium indicated that the subcutaneous administration of germanium dioxide or sodium germanate had a distinct erythropoietic action[1] and so was useful in the treatment of secondary and pernicious anemias. A later study indicated that a temporary increase in the number of erythrocytes per unit volume might be due merely to dehydration following the injection of large doses of colloidal GeO_2,[2] although this was before a clarification of the polymorphism of GeO_2[3] so that it is not known whether the soluble (hexagonal) or insoluble (tetragonal) form was administered in this or the earlier work. A single subcutaneous administration of 10.5 mg. of germanium/kg. (as GeO_2) has been shown not to be toxic, nor is a single intravenous injection of 12.6 mg. germanium/kg.,[4] but "excessive amounts" cause a marked drop in blood pressure and "toxic doses" cause a rise in *p*H of the blood and massive brown deposits in the organs.[1a]

(1) (a) L. Kast, H. M. Croll and H. W. Schmitz, *J. Lab. Clin. Med.*, **7**, 643 (1922); (b) J. L. Lenker, *Penn. Med. J.*, **26**, 86 (1922); (c) R. M. Parr, *Trans. Ill. Acad. Sci.*, **21**, 194 (1928); U. S. Patent 1,909,070.

(2) W. C. Hueper, *Am. J. Med. Sci.*, **181**, 820 (1931).

(3) A. W. Laubengayer and D. S. Morton, THIS JOURNAL, **54**, 2303 (1932).

(4) G. C. Harrold, S. F. Meck and C. P. McCord, *Ind. Med.*, **13**, 236 (1944).

The relatively easy preparation of organogermanium halides by the direct synthesis[5] has led to the synthesis of polymeric dimethylgermanium oxide,[6] which has a surprisingly high solubility in water in comparison with ethyl or phenylgermanium oxides. The immediate questions which arise are (1) does the $(CH_3)_2Ge<$ group undergo hydrolysis or oxidation *in vivo*, resulting in the liberation of toxic methyl groups, and (2) if the $(CH_3)_2Ge<$ group is stable under body conditions, does it exert a stimulating influence on red blood cell formation as does germanium ion? Complete answers to these questions would involve elaborate and exhaustive studies with separate groups of experimental animals in large number, but it was felt that some preliminary information might be gained by subcutaneous injection of an aqueous solution of dimethylgermanium oxide in experimental animals. In the absence of gross toxicity, the effect of the substance on blood composition could be followed by periodic determination of hemoglobin level and red cell count on the same group of animals.

Experimental

Dimethylgermanium oxide was prepared from dichloride,[6] distilled as the tetramer, and dissolved in water to a

(5) Rochow, THIS JOURNAL, **69**, 1729 (1947); **70**, 436 (1948).

(6) Rochow, *ibid.*, **70**, 1801 (1948).

concentration of 0.189 g. per ml., which is equivalent to 0.100 g. of germanium per ml. if the dissolved species is $(CH_3)_2Ge(OH)_2$. This solution was sterilized by boiling and was used throughout the tests.

In one early study[7] rats were given nutritional anemia by a six-week diet of whole milk rigorously protected from contamination with metals, and then controlled amounts of iron and other metals were fed. Combinations of metals were found more effective in correcting the anemia than iron or any other metal alone, as has also been shown by other investigators. In the present investigation, in order to evaluate germanium (as $(CH_3)_2GeO$) in the presence of all usual dietary factors, hamsters were kept on a diet of lettuce, carrots and prepared dry food in surplus quantity and were given the dimethylgermanium oxide by subcutaneous injection on the back of the head. Samples of blood were taken from the hamsters under minimal ether anesthesia by clipping a 2 × 3 mm. patch of loose skin from the upper inside surface of the hind leg, nicking a large vein in the underlying muscle, and withdrawing a drop of blood directly into the pipets used for duplicate determination of hemoglobin or red cell count. The skin then was closed with a sterile 5-0 nylon suture. The hamsters showed no ill effects from repeated ether anesthesia, but the local incisions produced scar tissue and blood clots in the vein which made it difficult to get later samples from the same locale. For this reason the number of reliable blood samples that could be obtained from each hamster was limited to four.

Hemoglobin was determined by dilution with 0.1 *N* hydrochloric acid in a Hellige hemometer. Red cell counts were made with a Spencer hemacytometer after dilution with Hayem's fluid in the usual way. While average values for hamsters are not readily found in the literature, preliminary experiments showed that hamster blood contains 16 to 19 g. of hemoglobin per 100 ml. of whole blood, and that the red cell counts range from 8.9 to 10.7 millions per mm.[3] It also was found from the preliminary work that injection of 0.5 to 1.0 ml. of the germanium solution (corresponding to 1 g. germanium/kg. of body weight) caused no local irritation nor any symptoms of toxicity noticeable within three weeks.

A group of fifteen hamsters of both sexes, all eight to twelve weeks old, was divided into three equal groups. The first was used for a control. Each animal of the second group was given 0.5 ml. of the solution of dimethylgermanium oxide and used for red cell counts on the first, second, third, fifth and eighth day after administration. Each animal of the third group also was given 0.5 ml. of solution, and then was used for hemoglobin determinations on the first, second, third and seventh day after administration. The results are given in Tables I, II and III, respectively (each figure is the average of two readings). During the tests and for six weeks thereafter (with the exception noted in Table III) the animals appeared to be in perfect health. They gained weight in normal fashion, developed no change in appearance, and seemed to enjoy normal vision.

TABLE I

HAMSTERS IN CONTROL GROUP

Animal, no.	Hemoglobin, g./100 ml. Initial	After days	
1	16.2	1	16.1
2	18.5	2	18.7
3	17.2	3	17.1
4	18.6	5	?
5	17.5	21	18.4
	Red cells, millions per cu. mm.		
5	7.8	2	8.5

Another group of nine hamsters was given graded doses of dimethylgermanium oxide (0.25, 0.50, 0.75 and 1.00 ml. of the standard solution) and used for red cell counts over a period of ten days. The results, which are given in Table IV, did not differ appreciably from the results obtained at a single dosage level; neither was there any toxic effect noticed in any of the animals.

(7) Beard and Myers, *J. Biol. Chem.*, **94**, 71 (1931).

TABLE II

RED CELL COUNT OF HAMSTERS GIVEN 0.5 ML. OF $(CH_3)_2GeO$ SOLUTION (ABOUT 1 G. Ge/KG. BODY WEIGHT)

Animal no.	Erythrocytes in millions/cu. mm. Before injection	Days elapsed	After injection
1	8.7	1	8.1
2	6.8	2	8.3
3	7.5	3	8.2
4	8.9	5	8.1
5	8.7	8	8.4

TABLE III

HEMOGLOBIN OF HAMSTERS GIVEN 0.5 ML. OF $(CH_3)_2GeO$ SOLUTION (ABOUT 1 G. Ge/KG. BODY WEIGHT)

Animal no.	Hemoglobin, g./100 ml. Before injection	Days elapsed	After injection
1	16.6	1	13.0
2	18.8	2	18.0
3	17.0	3	16.0
4	16.6	7	14.5
5	18.0	5[a]	..

[a] This animal died on the fifth day of unknown causes. Autopsy showed all organs to be normal in appearance, and no infection was apparent at the incision.

TABLE IV

RED CELL COUNT OF HAMSTERS GIVEN VARYING DOSES OF $(CH_3)_2GeO$

Animal no.	Dose, ml. of soln.	Erythrocytes in millions/cu. mm. Initial	Days elapsed	After injection
1	0.25	9.9	7	9.6
2	.25	10.7	10	10.8
3	.50	10.4	3	10.6
4	.50	9.7	7	8.9
5	.50	10.1	10	10.5
6	.75	9.0	1	9.4
7	.75	9.4	3	9.5
8	.75	9.4	7	10.0
9	1.00	8.9	1	8.9

In order to get a larger number of successive samples of blood from one animal than is possible with a hamster, a pair of male rabbits was used for a further experiment involving cumulative dosage of dimethylgermanium oxide. One rabbit was given 0.25 ml. of the standard solution intravenously through the marginal vein of the ear at the start of the experiment, 0.50 ml. on the third day thereafter, 0.75 ml. on the sixth day, 1.00 ml. on the tenth day, 1.25 ml. on the 13th day, 1.50 ml. on the 18th day and 1.75 ml. on the 21st day; no germanium was given to the

TABLE V

RED CELL COUNT OF RABBITS

Days	Dose, ml.	Erythrocytes, millions/cu. mm.	RBC of control rabbit (no Ge)
0	0.25	7.2	5.8
3	0.50	6.3	5.7
6	0.75		
10	1.00	6.7	6.6
13	1.25	6.0	
18	1.50	6.3	
21	1.75	6.2	7.1
24	0	7.3	7.1

other rabbit. Samples of blood for red cell counts were drawn from the same ear vein immediately before each injection of germanium, and the results are given in Table V. The first rabbit received a total of 13.2 g. of $(CH_3)_2Ge(OH)_2$, which corresponds to a total dose of 7.0 g. of germanium (or 3.8 g. germanium per kg. of body weight) in the increasing doses, but showed no toxic effects whatever.

Discussion

The fact that no local or systemic toxicity was observed in any of the animals receiving dimethylgermanium oxide indicates that the organometallic grouping remains intact, in keeping with the marked resistance of the same group to oxidation or hydrolysis *in vitro*.[5] A more decisive answer could be obtained by determining the germanium excreted as dimethylgermanium oxide and as germanium oxide over a considerable period after injection; the total germanium could be determined spectrographically, but a good method for differentiating between the inorganic and the organometallic germanium at the expected levels has not yet been developed.

While there is considerable variation between the hemoglobin levels of different control hamsters, the level for a particular animal is quite constant over the relatively short time of the tests (Table I). This is the reason for giving the results for individual animals, rather than an average for the group. Hemoglobin determinations with a Hellige hemometer are subject to an error of $\pm 5\%$, however, and while the spread between the duplicate determinations usually was less than this and sometimes as little as $\pm 1.5\%$, no significance can be attached to a change of less than 10% during the test. The red cell counts are subject to about the same error, and while most of the duplicate determinations checked closely, no dependence can be placed on a change of less than 10%, or about 800,000 erythrocytes per cu. mm.

With the limits defined in this way, it must be concluded that the subcutaneous injection of dimethylgermanium oxide does not markedly influence the normal hemoglobin level of the animals used, nor does it change the normal concentration of erythrocytes. It appears that there may be an initial depression of both the hemoglobin and red cell values for hamsters for a period of one to three days after injection, followed by a recovery. A similar marginal effect was noticed in the experiment with rabbits.

Summary

The subcutaneous administration of an aqueous solution of dimethylgermanium oxide to small animals, up to a level of 1 g. of germanium per kg. of body weight either in one dose or cumulatively, produces no noticeable toxic effects that might be expected to occur if the $(CH_3)_2Ge$ group underwent *in vivo* hydrolysis or oxidation. The normal hemoglobin and red cell contents of the blood are not appreciably changed by the same dose.

CAMBRIDGE, MASS. RECEIVED NOVEMBER 21, 1949

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF OREGON STATE COLLEGE]

The Exchange Reaction of Sulfur Dioxide with Concentrated Sulfuric Acid[1]

BY T. H. NORRIS

The exchange of oxygen atoms between compounds containing sulfur(IV) and sulfur(VI) was first investigated by Voge[2] using radioactive sulfur. He observed no exchange in thirty-six hours at 100° between sulfite and sulfate in either basic or 0.1 *N* acid solution. He did observe a slow exchange at 335° between sulfur dioxide and sulfur trioxide gases, which was accelerated by the presence of water, or of platinized asbestos.[3] Some experiments[4] on the exchange of sulfur dioxide with concentrated, radioactive sulfuric acid have been performed and the results, while somewhat lacking in internal consistency, indicate roughly: (1) at room temperature, negligible exchange in forty-eight hours; (2) at 100°, 5% exchange in forty-eight hours; (3) at 280°, complete exchange in less than five hours.

The last results, when compared with those for the gas phase reaction on the one hand, and the approximately neutral aqueous reaction on the other, are evidently of considerable interest. Since, unfortunately, they are rather rough and qualitative, it was felt that they would bear repetition and extension. The present report, accordingly, presents further work on the exchange: $SO_2 + H_2S^*O_4$ (concd.) $\rightleftarrows S^*O_2 + H_2SO_4$ (concd.). It has been found that the rate is conveniently measurable in the range 160 to 210°, with a normal temperature coefficient, confirming, in a general way, Harmon's[4] results, except for his rate at 100°, which is much too high.

(1) Published with the approval of the Oregon State College Monographs Committee. Research Paper No. 144, Department of Chemistry, School of Science.

(2) Voge, THIS JOURNAL, **61**, 1032 (1939).

(3) The kinetics of the gas phase exchange, $SO_3 + S^*O_3 \rightleftarrows S^*O_3 + SO_3$, have since been investigated in detail (J. L. Huston and T. H. Norris, to be published). The rate, for intensively dried gases, in Pyrex, is conveniently measurable in the range 400–440° and has a normal temperature coefficient. The reaction is heterogeneous and strongly catalyzed by water (as Voge indicated), but the data are irreproducible and involved. Contrary to Voge's postulate, the rate-determining step seems not to be $SO_3 \rightleftarrows SO_3 + \frac{1}{2}O_2$.

(4) K. M. Harmon, Master's Thesis, University of California, Berkeley, 1944.