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# The Metabolic Fate of Some Silicon-Containing Carbamates[1]

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After ingestion, bis(hydroxymethyl)dimethylsilane dicarbamate (III), (hydroxymethyl)dimethyl-*n*-propylsilane carbamate (IV), and bis(hydroxymethyl)methyl-*n*-propylsilane dicarbamate (silameprobamate) (V) are absorbed and eliminated in the urine of rats. III is eliminated unchanged. IV is metabolized; bis(hydroxymethyl)tetramethyldisiloxane dicarbamate (VI) was isolated from the urine. V is also metabolized; two products isolated from the urine were a disiloxane VII as the minor component and bis(hydroxymethyl)(2-hydroxypropyl)methylsilane dicarbamate (VIII) as the major component. The data indicate that dealkylation is one of the metabolic paths for elimination of organosilicon compounds.

Although organosilicon compounds are used both in commerce and in medicine, little is known about their metabolic fate. Paul and Pover[3] have provided evidence that methyl ω-(trimethylsilyl)dodeconate and trimethylsilylhexadecane are absorbed from the gastrointestinal tract of rats. Dow Corning[4] has reported that [$^{14}$C]methylpolysiloxane is not excreted as $^{14}CO_2$. Our own interest in the metabolism of organosilicon compounds was stimulated by the lack of oral activity of silameprobamate (V), although it showed the same $ED_{50}$ (rotating rod) as meprobamate (I) when it was dosed intraperitoneally.[5] It was felt that this difference in activity could be due either to a lack of absorption of the silicon compound when dosed orally or to a different detoxification pathway.

The metabolism of I itself has been studied by a number of investigators.[6] Oxidation of the propyl group provides the major pathway of detoxification. Carboxymeprobamate, ketomeprobamate, and hydroxymeprobamate (II) have been identified as metabolites (see Scheme I). The relative amounts of these metabolites vary with the species; however, the alcohol II is the major detoxification product.

SCHEME I

$$\underset{\text{I}}{CH_3CH_2CH_2C(CH_3)(CH_2OCONH_2)_2} \rightarrow \underset{\text{II}}{CH_3CHOHCH_2C(CH_3)(CH_2OCONH_2)_2} + CH_3COCH_2C(CH_3)(CH_2OCONH_2)_2 + HO_2CCH_2CH_2C(CH_3)(CH_2OCONH_2)_2$$

This study is concerned with the identification of the metabolites appearing in the urine arising from the oral dosing of some silacarbamates, bis(hydroxymethyl)dimethylsilane dicarbamate (III), (hydroxymethyl)dimethyl-*n*-propylsilane carbamate (IV), and silameprobamate (V).

$$\underset{\text{III}}{CH_3Si(CH_3)(CH_2OCONH_2)_2} \qquad \underset{\text{IV}}{n\text{-}C_3H_7Si(CH_3)_2CH_2OCONH_2}$$

$$\underset{\text{V}}{n\text{-}C_3H_7Si(CH_3)(CH_2OCONH_2)_2}$$

In our previous work,[5] we were able to show that III showed no pharmacological activity (rotating rod test) at intraperitoneal dose levels up to 500 mg/kg. In the present study, when III was orally dosed in rats, 53% of the ingested material was isolated from the urine as the crystalline unaltered compound. No metabolites were observed for this particular compound.

Compound IV showed an $ED_{50}$ of 158 (148–169) mg/kg ip.[5] After oral dosing of IV in rats, about 90% of the ingested silicon could be detected in the urine within 4 days. In the ethyl ether extract of the urine, no unchanged IV could be detected. From an ethyl acetate extraction, there was obtained a silicon-containing oil, which was subjected to chromatographic separation. A white crystalline solid, mp 68–70°, was isolated. The nmr spectrum of this material showed two sharp singlets and a broad band, which, from the chemical shifts and areas under these bands, suggested that the solid is the disiloxane VI. The infrared spectrum and the elemental analysis of this material are in agreement with this structure assignment. This metabolite accounts for 29% of the silicon of the ingested silacarbamate IV. No other silicon metabolites were detected.

$$\text{IV} \longrightarrow \underset{\text{VI}}{NH_2COOCH_2Si(CH_3)_2OSi(CH_3)_2CH_2OCONH_2}$$

After oral dosing of silameprobamate, 60–90% of the ingested silicon was found in the urine within 3 days. Extraction and chromatographic separation afforded a solid material (mp 54–58°) and a viscous oil. Unfortunately, neither of these substances could be obtained in an analytically pure form.

(1) This research was supported by Public Health Research Grant GM13914 from the National Institute of General Medical Sciences.

(2) Alfred P. Sloan Fellow, 1965–1967.

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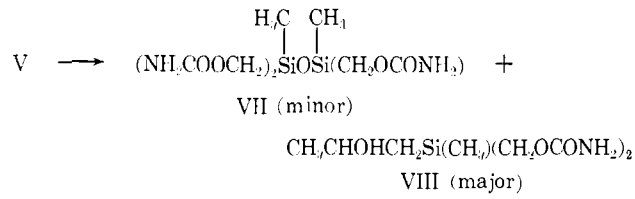
(6) (a) B. J. Ludwig, J. F. Douglas, L. S. Powell, M. Meyer, and F. M. Berger, *J. Med. Pharm. Chem.*, **3**, 53 (1961); (b) F. M. Berger, *J. Pharmacol. Exptl. Therap.*, **112**, 413 (1954); (c) B. W. Agranoff, R. M. Bradley, and J. Axelrod, *Proc. Soc. Exptl. Biol. Med.*, **96**, 261 (1957).

On the basis of spectral evidence, the solid can be tentatively assigned the structure of the disiloxane VII. The chemical shifts in the nmr spectrum of this material are almost identical with those of the nmr of the disiloxane VI, except that the ratio of the area under the upfield singlet to that under the downfield singlet was 6:8, rather than 4:11, as observed for VI. The infrared spectrum showed absorption characteristics of the $CONH_2$, $SiCH_3$, and SiOSi functions.[7]



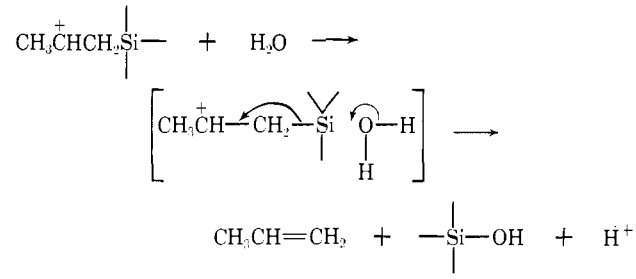
V ⟶ $(NH_2COOCH_2)_2SiOSi(CH_3OCONH_2)$ + VII (minor)

$CH_3CHOHCH_2Si(CH_3)(CH_2OCONH_2)_2$ VIII (major)

A combination of chemical and spectral evidence was used to assign tentatively the structure of the hydroxysilameprobamate VIII to the oil. The oil is soluble in water, gives positive iodoform and ceric nitrate tests, and contains 10.5% silicon. Structure VIII should contain 11.2% silicon and should also give positive iodoform and ceric nitrate tests. The infrared spectrum of this compound showed a broad band at 2.8–3.1 $\mu$, which can be assigned to the combined absorption of the OH and $NH_2$ groups. Absorption was also observed at 5.85 and 6.25 (characteristic of the carbamate function), 7.95 ($SiCH_3$), and 9.2 $\mu$ (C–O). The characteristic SiOSi absorption at 9.5 $\mu$ was absent.

The nmr spectrum of the oil in $D_2O$ is summarized in the Experimental Section. There were observed two singlets ($SiCH_3$ and $SiCH_2O$) and three peaks in the alkyl region (overlapping doublets, $CH_3CHOHCH_2Si$). The multiplet for the proton on the hydroxyl carbon ($CH_3CHOHCH_2Si$) is partly masked by the singlet of the $SiCH_2O$ group but is evident slightly upfield from the singlet. The relative areas under these three groups of bands are in the ratio of 3.0:5.2:5.0. The acidic protons can be expected to exchange with $D_2O$ and, indeed, a strong peak at $\delta$ 4.65 (water) was evident.

From these data, it can be concluded that dealkylation, as well as oxidation, is one of the metabolic pathways for organosilicon compounds. It should be pointed out that the loss of an alkyl group from an organosilicon compound is not an unexpected observation. Oxidative hydroxylation at the $\omega$-1 carbon atom of alkyl groups is well known.[8] With a propylsilane, such oxidation would occur $\beta$ to the silicon. It can be expected that, during the course of the metabolic oxidation, an electron-deficient center (illustrated as a carbonium ion below) would be generated. In the laboratory, the formation of an electron-deficient center $\beta$ to a silicon atom can result in dealkylation.[9] Although evidence is lacking, it is probable that the dealkylated metabolites were actually silanols [*e.g.*, $CH_3(NH_2CO_2CH_2)_2SiOH$, in the case of V], which would be water soluble and which would readily condense[10] to the observed disiloxanes under the conditions employed for isolation.



$CH_3\overset{+}{C}HCH_2\overset{|}{Si}-$ + $H_2O$ ⟶

$\left[CH_3\overset{+}{C}H-CH_2-\overset{|}{Si}-\overset{|}{O}-H\right]$ ⟶

$CH_3CH=CH_2$ + $-\overset{|}{Si}-OH$ + $H^+$

In summary, it has been shown that the carbamates III–V are absorbed from the gastrointestinal tract of rats and that IV and V are metabolized. For IV, only the dialkylated metabolite VI was found in the urine. The detoxication path of silameprobamate (V), involving $\omega$-1 oxidation of the propyl group, appears to be similar to that for meprobamate (I). The major isolated metabolite for V was the hydroxy compound VIII, which is analogous to the major metabolite from I.

## Experimental Section[11]

The preparation of the carbamates III–V has been described in a previous paper.[5]

**Dosing and Urine Collection.**—Female rats (Long-Evans), 250–300 g, were starved overnight, then individually orally dosed with the desired compound. The animals were housed separately in metabolism cages constructed to allow separate collection of urine and fecal material. Food and water were given, *ad libitum*, immediately after dosing. The urine was pooled and stored under toluene. Silicon-containing materials were not observed in the toluene layer. The fecal material was not investigated.

**Silicon Analysis.**—The pooled urine was filtered through Celite. The volume was measured, a 25-ml aliquot was transferred to a Pt crucible, and 25 ml of concentrated $H_2SO_4$ was added carefully. The mixture was digested 20–30 min on a hot plate. In some cases, a few drops of fuming nitric acid was added to aid the oxidation. The excess acid was fumed off using an open flame, with care being taken that the liquid did not splatter. The crucible was then flamed to red heat, cooled, and weighed. A few drops of HF was added. The crucible was again taken to dryness and flamed, cooled, and reweighed. The difference between the two weights was taken as the amount of $SiO_2$ present. All analyses were run in triplicate, and the results are reported as the extrapolated value to the total volume.

Normal rat urine contains an average of 6 mg of $SiO_2$/25 ml as determined by this method. The weight of the $SiO_2$ obtained from the urine of the dosed animals was corrected by this value. Unfortunately, elimination of $SiO_2$ by a normal rat is extremely variable (0–16 mg/25 ml); therefore, the correction can only be an approximation.

**Thin Layer Chromatographic Analysis.**—Development of the plates was carried out using toluene–methanol (2:1), and visualization of the plates was generally accomplished using 1% iodine in methanol. Visualization of the carbamates, however, was effected by warming the plates in an oven at 90° and then

(7) The infrared absorption of the disiloxane group is in the 9.5-$\mu$ region and is very broad and intense. Absorption for C–O is generally observed in the 9.2-$\mu$ region, but is sharper and less intense. In this case, both bands were observed in the spectrum.

(8) (a) R. T. Williams, "Detoxication Mechanisms," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1959, p 593 ff; (b) E. W. Maynert and H. B. vanDyke, *Pharmacol. Rev.*, **1**, 217 (1949).

(9) For a summary of $\beta$-elimination reactions, see C. Eaborn, "Organosilicon Compounds," Academic Press Inc., New York, N. Y., 1960; and V. Bazant, V. Chvalovsky, and J. Rathousky, "Organosilicon Compounds, Part I," Academic Press Inc., New York, N. Y., 1965.

(10) The ease of condensation of silanols to disiloxanes depends upon the hindrance around the Si atom. For example, trimethylsilanol is very difficult to isolate and condenses very readily to hexamethyldisiloxane. Triethylsilanol can be distilled but is readily converted to hexaethyldisiloxane under dehydrating conditions. See ref 9 for general reviews of this area.

(11) Melting points are corrected and were determined on a Fisher-Johns melting point apparatus. C, H, and N analyses were performed by the Berkeley Microanalytical Laboratory and Si analyses in this laboratory. Infrared spectra were obtained using a Beckman IR-5 spectrophotometer. The nmr spectra were obtained using a Varian A-60 spectrometer. Values are reported downfield from TMS in $\delta$ (ppm) with $CHCl_3$ or $H_2O$ as an internal standard.

immersing them in a chlorine atmosphere for at least 10 min. After the immersion, air was blown across the plate to remove the unbound chlorine and the plates were sprayed with a 2% solution of potassium iodide containing thioline. Control runs showed that this procedure was specific for the urinary carbamates.

**Bis(hydroxymethyl)dimethylsilane Dicarbamate (III).**—A total of 1.5 g of III, mp 104–106°, was administered to three rats in a suspension of gum tragacanth. The urine was collected for 48 hr. Analysis for silicon indicated that approximately 70% of the administered dose was present in the urine. The urine was extracted continuously for 12 hr with ether. Removal of the ether under vacuum and crystallization of the resulting solid from water afforded 0.80 g (53%) of the unchanged dicarbamate, mp 99–101°, mmp (with III) 98.5–101°. The infrared spectrum of this material was identical with that of III.

**(Hydroxymethyl)dimethyl-*n*-propylsilane Carbamate (IV).**—A total of 7.8 g of IV was administered neat to 17 rats, and their urine was collected for 4 days. Analysis of the urine for silicon indicated that approximately 90% of the dosed silicon was present. The urine was extracted overnight with ethyl acetate. The solvent was removed under vacuum, and the residue was dissolved in acetone and filtered to remove the precipitated urea. Evaporation of the acetone afforded 5.3 g of a dark oil. Chromatography of the oil through 200 g of alumina, activity III, was carried out using the solvent scheme of chloroform–ether (1:1), 100 ml, and ether, 200 ml. Eighty fractions were collected. Tlc of these fractions indicated that only one carbamate (in fractions 43–78) was present. Combination of these fractions and crystallization from ether–petroleum ether (bp 30–60°) yielded 1.8 g (29%) of the dicarbamate disiloxane VI, mp 68–70°.

*Anal.* Calcd for $C_8H_{20}N_2O_5Si_2$: C, 34.25; H, 7.20; N, 9.99. Found: C, 34.43; H, 7.06; N, 9.82.

The nmr spectrum of VI in $CHCl_3$ showed a singlet at $\delta$ 0.3 ($SiCH_3$), a singlet at 3.8 ($SiCH_2OCONH_2$), and a broad band at 5.2 ($CONH_2$). The $CHCl_3$ proton was used as the internal standard. The two singlets showed an area ratio of 4:11. The significant bands in the infrared spectrum ($CHCl_3$) were 2.85, 2.95 ($NH_2$), 5.85, 6.25 ($CONH_2$), 7.95 ($SiCH_3$), and 9.5 $\mu$ (SiOSi). In another run, extraction of the urine with ether, followed by tlc analysis of the resulting oil, failed to reveal the presence of unaltered carbamate. Control runs indicated that this method could detect about 2% of the dosed amount.

**Bis(hydroxymethyl)methyl-*n*-propylsilane Dicarbamate (Silameprobamate) (V).**—Twelve grams of V was dosed to 62 rats and the urine was collected for 3 days. Silicon analysis at the end of this period indicated that approximately 80% of the ingested silicon had been eliminated. The urine was extracted overnight with ethyl acetate. Removal of the ethyl acetate and the urea afforded 8.6 g of a dark oil. Chromatography of this material was carried out using 400 g of alumina, activity III. Sixty 10-ml fractions were collected, using the following solvent scheme: benzene–ethyl acetate (1:1), 150 ml; benzene–ethyl acetate (1:2), 50 ml; ethyl acetate, 50 ml; ethyl acetate–acetone (1:1), 50 ml; acetone, 50 ml; acetone–methanol (1:1), 50 ml; and methanol, 200 ml. Thin layer chromatography of the eluted fractions showed the presence of two carbamates: $R_f$ 0.53 (minor component), appearing in fractions 19 and 20, and $R_f$ 0.37 (major component), appearing in fractions 24–54.

The first component, $R_f$ 0.53, 20 mg, was a white solid with mp 54–58°. The nmr spectrum of this material in $CHCl_3$ showed three bands: $\delta$ 0.30, singlet; 4.0, singlet; and 5.2, a broad band. The area ratio under the two singlets was 6:8.4. The infrared spectrum ($CHCl_3$) showed the significant peaks at 2.85, 3.0, 5.85, 6.3, and 7.95, and a broad band at 9.5 $\mu$.

The second component, $R_f$ 0.37, 2.3 g, was an oil. This material was combined and rechromatographed through alumina, activity IV, using ethyl acetate as solvent. The nmr of the eluted material, in $D_2O$ showed a singlet at $\delta$ 0.2 (relative area, 3.0), three peaks (but not a triplet) at 1.0, 1.15, and 1.25 (combined area, 5.2), a singlet at 3.9, and a multiplet starting at 4.0 (combined area under the singlet and the multiplet, 5.0). The infrared spectrum (thin film) showed a broad and intense absorption in the 2.9-$\mu$ region and other significant bands appearing at 5.85, 6.25, 9.4 (sharp), and 7.95 $\mu$. Using the Beckman IR-4 spectrophotometer and LiF optics, the broad band at 2.9 $\mu$ could not be resolved. The eluted oil gave a positive iodoform test and a positive ceric nitrate test but failed to yield a solid derivative with $\beta$-naphthyl isocyanate.

*Anal.* Calcd for $C_3H_9O_3N_2Si$: Si, 11.2. Found: Si, 10.5.

In another run, the urine was first extracted 12 hr with ether. Tlc analysis of the ether extract showed no evidence of silameprobamate. Control runs indicated that 10 mg of silameprobamate in 100 ml of urine (about 2% of the dose) could be detected.

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# Compounds Acting on the Central Nervous System. VII. Studies in 1-Pyridyl-4-substituted Piperazines. A New Class of Anticonvulsants

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A number of 1-pyridyl-4-substituted piperazines have been synthesized and evaluated for their pharmacological action. A number of 1-(3-amino-4-pyridyl)-4-phenylpiperazines have been shown to possess marked anticonvulsant and antireserpine properties. Their structure–activity relationship is discussed. In particular, 1-(3-amino-4-pyridyl)-4-(3-trifluoromethylphenyl)piperazine has shown promising anticonvulsant activity.

In a study reported earlier[1,2] it was found that the pattern of biological activity of 3,4- and 2,3-diaminopyridines was greatly changed when one of the amino groups was substituted by a $\beta$-arylalkyl- or $\beta$-azacycloalkane radical, and a number of new activities not associated with the parent compounds appeared in the resulting derivatives, which included hypotensive, antipyretic, anticonvulsant,[3] and antiinflammatory[4] activities. In continuation of this study of substituted diaminopyridines, making one of the amino groups part

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