Metabolic Fate of Phenyltrimethylsilane and Phenyldimethylsilane[1]

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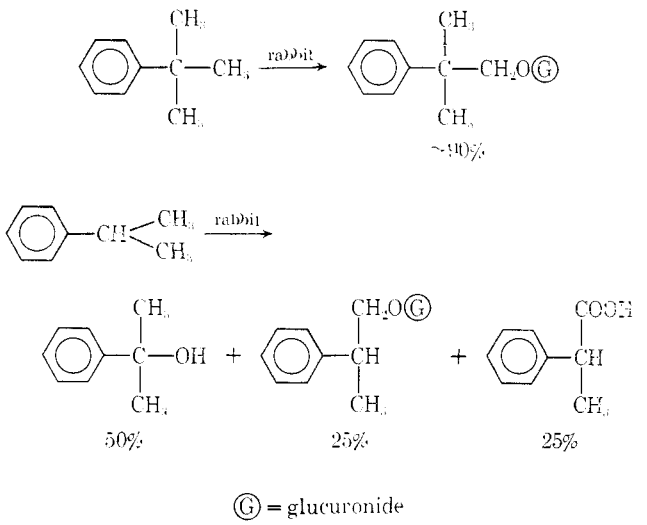
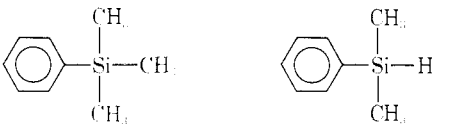
After ingestion (rat), phenyltrimethylsilane is absorbed and eliminated in the urine as both phenyl- and methyl-hydroxylated metabolites. Phenyldimethylsilane is also absorbed, but hydroxylation occurs on the silicon at the silicon–hydride position. The data indicate that the silicon-phenyl bond is stable *in vivo*, while the silicon–hydride bond is not.

The urinary metabolic end products of aromatic compounds have been studied by a number of investigators.[3] In general, these compounds undergo hydroxylation either on the aromatic ring or on the alkyl substituent. Germane to this report is the work of Williams on the fate of *t*-butylbenzene[4] and isopropylbenzene.[5] After being given orally to a rabbit, each of these compounds is hydroxylated on the alkyl portion of the molecule and eliminated as a glucuronide conjugate or as a higher oxidized product. Williams did not report any aromatic ring-hydroxylated metabolites.[6]



The title compounds were chosen for study because they contain two key structural features common to many organosilicon compounds—the silicon–phenyl bond and the silicon–hydride bond. In addition, since little work has been reported in the area of organosilicon metabolism,[7] these two structures provide a suitable starting point for future work in the area.

The goal of the project was the identification of the major urinary metabolites of the title compounds I and II, as well as the obtaining of data concerning the absorption and elimination of these compounds after oral dosing.



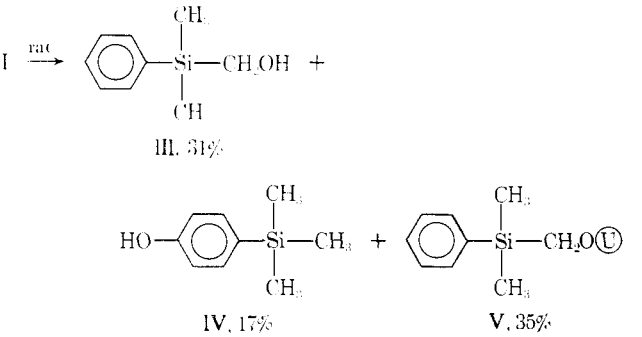
I II

For convenience, male Long Evans rats (300–400 g) were used and the compounds were administered as single, neat doses with a stomach tube. Only the urinary metabolites were studied; no attempt was made to provide an over-all material balance.

For the purpose of tracing the metabolites, radioactive labeling of the dosed compounds was necessary. Because silicon has no suitable isotope for this type of study, the [14-C]methyl–silicon label was used. In using this type of satellite labeling it must be assumed that the silicon–methyl group remains intact *in vivo* and is eliminated in the urine without cleavage. The method therefore requires that the final metabolic product(s) be characterized structurally before conclusions can be made from radioactive-counting data about the metabolic fate of the silicon atom.

Phenyltrimethylsilane (I).—After the oral dosing of I, 32–40% of the radioactivity appeared in the urine within the first 24-hr period. Another 8–20% appeared during the second 24-hr period, and the activity dropped to trace amounts after the second day. In one run, the respired CO_2 was collected and shown to be inactive.

Pooled urine from a number of rats was extracted with EtOAc, and the concentrated extract was subjected to tlc separation procedures. Three radioactive metabolites were isolated and characterized: (hydroxymethyl)dimethylphenylsilane (III), *p*-trimethylsilylphenol (IV), and an unknown conjugate of III (V).



In another run, using an isotopic dilution technique, 3% of the total urinary activity was shown to be from hexamethyldisiloxane. One of the metabolites, *p*-trimethylsilylphenol (IV), is known to undergo re-

(1) This research was supported by Public Health Research Grant GM 15860 from the National Institute of General Medical Sciences.

(2) Alfred P. Sloan Fellow, 1965–1969.

(3) For a general reference see W. H. Fishman, "Chemistry of Drug Metabolism," Charles C Thomas, Publisher, Springfield, Ill., 1961.

(4) D. Robinson and R. T. Williams, *Biochem. J.*, **59**, 159 (1955).

(5) D. Robinson, J. N. Smith, and R. T. Williams, *ibid.*, **59**, 153 (1955).

(6) Preliminary evidence from this laboratory indicates that ring hydroxylation also occurs with *t*-butylbenzene (rat).

(7) R. J. Fessenden and C. Ahlfors, *J. Med. Chem.*, **10**, 810 (1967).

arrangement to trimethylsiloxybenzene (VI).[8] This compound, in turn, reacts with water to form phenol and trimethylsilanol, which undergoes dehydration to hexamethyldisiloxane. It is felt that the small amount of hexamethyldisiloxane found was due to the chemical rearrangement and cleavage rather than to a biological process.

$$\underset{\text{IV}}{p\text{-HOC}_6\text{H}_4\text{Si(CH}_3)_3} \xrightarrow{\Delta} \underset{\text{VI}}{\text{C}_6\text{H}_5\text{OSi(CH}_3)_3} \xrightarrow{\text{H}_2\text{O}} \text{C}_6\text{H}_5\text{OH} +$$

$$(\text{CH}_3)_3\text{SiOH} \xrightarrow{-\text{H}_2\text{O}} (\text{CH}_3)_3\text{SiOSi(CH}_3)_3$$

Although the tlc isolation procedure did not yield analytically pure materials, the procedure did concentrate the radioactive material to a point where a combination of ir, nmr, and mass spectral data provided sufficient evidence for structural assignment. As further evidence for the assignment of structures to the radioactive metabolites, the phenol IV and the hydroxymethyl compound III were synthesized by independent routes and their spectra were compared to those of the isolated metabolites.

In the case of the unknown conjugate, the structure of the conjugate was not determined; the structure of the silicon part of the compound is based upon spectral evidence. This metabolite clearly is not III or IV as determined by tlc R_f values. The nmr spectrum indicated the presence of silicon–phenyl and silicon–methyl groups. The ratio of the silicon–phenyl to silicon–methyl protons in the nmr was approximately 5 to 6. The mass spectrum of this material (direct probe) showed a base peak at m/e 135 which can be assigned to the ion, $C_6H_5Si(CH_3)_2^+$. These data indicate that the metabolite contains a conjugated hydroxymethyl–silicon group rather than a conjugated hydroxylated ring.

Phenyldimethylsilane (II).—After oral dosing of II, 88% of the radioactivity appeared in the urine within 36 hr. After the pooled urine was made slightly acidic, the activity was easily extracted (Et_2O). A mass spectrum of the crude concentrated extract showed a base peak at m/e 137 (36% of the total ionizing current). The synthetic silanol VII also shows a base peak at m/e 137 (95% of the total ionizing current), but the corresponding disiloxane VIII does not.

The crude extract was purified by the tlc procedure. Two active spots were observed, 90% on the plate and 10% at the origin. Collection and spectral analysis of the 90% spot showed this material to be diphenyltetramethyldisiloxane (VIII).

$$\text{II} \xrightarrow{\text{rat}} \underset{\text{VII, } \sim 90\%}{\text{C}_6\text{H}_5\text{Si(CH}_3)_2\text{OH}} \xrightarrow[\text{tlc}]{-\text{H}_2\text{O}} \underset{\text{VIII}}{\text{C}_6\text{H}_5\text{Si(CH}_3)_2\text{OSi(CH}_3)_2\text{C}_6\text{H}_5}$$

From the mass spectral data before and after purification, it is clear that the metabolite was phenyldimethylsilanol (VII) (or a conjugate of the silanol), which underwent condensation to the disiloxane VIII during purification.

Unlike the cases of isopropylbenzene, *t*-butylbenzene, and trimethylphenylsilane, other hydroxylated products were not observed. We conclude that the silicon–hydride is not stable *in vivo* and that this bond is the principal site of metabolic attack on this compound.

Experimental Section[9]

Phenyldimethyl[^{14}C]methylsilane (I).—Phenyldimethylchlorosilane, bp 48–52° (3 mm), was prepared in 63% yield by the reaction of 1.0 mole of PhMgBr with 4.0 moles of dimethyldichlorosilane. To 0.2 g (8.3 mmoles) of Mg in 8 ml of dry Et_2O was added 1.0 g (6.9 mmoles) (*ca.* 50 μCi) of [^{14}C]MeI. The mixture was heated at reflux for 30 min. To this Grignard reagent was added 2.4 g (14 mmoles) of $PhSiClMe_2$ and the mixture was heated at reflux for 2 hr. Then 10 ml of 0.5 *N* HCl was added slowly. The organic material was extracted (Et_2O) and dried (Na_2SO_4). To the Et_2O solution was added 1.0 g of nonradioactive I. Fractional distillation through a 15.2-cm glass helices packed column yielded 1.52 g (49%) of the product, bp 164–165°, with an activity of 15.5 μCi/g. In repeat runs the yields were 47–69% with levels of activity of 23.6–34.5 μCi/g. Prior to dosing, the material was further diluted with nonradioactive I.

Phenylmethyl[^{14}C]methylsilane (II).—Phenylmethylchlorosilane, bp 50° (3 mm), was obtained in 52% yield from PhMgBr and methyldichlorosilane. Using the procedure described above, the chlorosilane was added to [^{14}C]MeMgI to yield 1.38 g (41%) of the active product (II), bp 151–153°, 20.5 μCi/g.

Comparison Compounds.—(Hydroxymethyl)dimethylphenylsilane[10] and *p*-trimethylsilylphenol[11] have been prepared previously in our laboratory. Dimethylphenylsilanol was obtained from the hydrolysis of an Et_2O solution of phenyldimethylchlorosilane. Et_2O was removed using a rotary evaporator and the residue was used directly for spectral analysis. This silanol was heated to effect condensation to the diphenyltetramethyldisiloxane, bp 190° (10 mm).[12]

Dosing, Elimination, and Extraction. A. Phenyltrimethylsilane (I).—A male Long Evans rat (300–400 g) was given a single oral dose of 0.4 ml (5.3 μCi) of I by means of a stomach tube. The rat was placed in a metabolism cage and allowed food and water *ad libitum*. The urine and the fecal material were collected separately for each 24-hr period. Only the urinary metabolites were investigated. Within the first 24 hr, 1.8 μCi (34%) appeared in the urine, and, in the second 24 hr, 0.85 μCi (16%). On the third and fourth days only trace amounts of activity could be detected. A total recovery of 50% (2.65 μCi) was effected. For the isolation work, the first 48 hr of urine of 43 rats was collected. The per cent of dosed activity eliminated by individuals in this group varied from 32 to 40% on the first day and 8 to 20% on the second.

In one experiment, a dosed rat was placed in a cage equipped for the collection of CO_2 by passing the respired air through NaOH soluion. No $^{14}CO_2$ could be detected.

A number of extraction procedures were tried with varying degrees of success. Although BuOH was an effective solvent for the extraction, large amounts of nonactive organic material, which interfered with the final purification, were also extracted. Et_2O was not effective. The use of continuous extraction was explored but was discarded because of emulsion formation.

The pooled urine from six to ten rats (50 ml) was filtered through glass wool then placed in a separatory funnel and extracted with ten 200-ml portions of EtOAc. By this procedure, 85–90% of the activity was extracted from the urine. EtOAc was removed by a rotoevaporator at room temperature. No activity was lost in this concentration. The residue was taken directly into the tlc separation procedure.

B. Phenyldimethylsilane (II).—The procedure described for I was also used for II. The rats were given 0.2 ml (3.67 μCi) of II and eliminated 3.24 μCi (88%) of the dosed activity in the urine within 36 hr. Oral dose levels of 0.3–0.5 ml of II were toxic. No attempt was made to assay for respired $^{14}CO_2$.

(8) J. L. Speier, *J. Am. Chem. Soc.*, **74**, 1003 (1952).

(9) A Packard EX-314 scintillation counter was used for all radioactive measurements. The scintillation solution contained toluene–ethanol (80:20) and 4.4 g/l. of Packard Pre-Mix M. The aliquot counted was either 50 or 100 μl. The cpm were converted to dpm and expressed in this report as μCi. The ir spectra were obtained using a Beckman IR7 equipped with a beam condenser and micro cell, the nmr spectra using a Varian HA-60 IL instrument, and the mass spectra using a modified CEC-103.

(10) R. J. Fessenden and M. D. Coon, *J. Med. Chem.*, **9**, 262 (1966).

(11) R. J. Fessenden, K. Seeler, and M. Dagani, *J. Org. Chem.*, **31**, 2483 (1966).

(12) W. H. Daudt and J. F. Hyde, *J. Am. Chem. Soc.*, **74**, 386 (1952).

The pooled urine from nine rats was acidified to pH 2–8 and extracted with two 100-ml portions of ether. The Et_2O solution was dried (Na_2SO_4), then concentrated with a rotoevaporator. Over 90% of the activity was extracted from the urine. The Et_2O concentrate was taken directly into the mass spectrometer (see below).

Isolation and Identification of Urinary Metabolites. A. Phenyltrimethylsilane (I). Hexamethyldisiloxane.—To the crude urine from three rats was added 100 ml of ether containing 1.0 g of nonlabeled hexamethyldisiloxane. After acidification, the urine was extracted once. The ethereal solution was concentrated to 25 ml, and a portion was subjected to glpc separation. The peak corresponding to the hexamethyldisiloxane was collected and counted. Of the total urinary activity, 3% could be accounted for as hexamethyldisiloxane.

Extracted Metabolites.—An aliquot (0.256 μCi) from the EtOAc concentrate was spotted on a tlc plate (silica gel) and developed with ether–petroleum ether (30–60°) (1:1). Active spots were found at R_f 0.68 (0.044 μCi, 17%), 0.56 (0.079 μCi, 31%), and the origin (0.090 μCi, 35%). The first two compounds were separated on preparative tlc plates and were removed from the silica gel with Et_2O. The compounds at the origin on these plates were removed from the silica gel with MeOH and were rechromatographed with EtOAc–PrOH (1:1). One active spot (R_f 0.09) was observed and this compound also was isolated by preparative tlc. Numerous other spots were observed in these tlc runs. Since they did not show activity, they were ignored.

This isolation procedure did not yield analytically pure material. However, the metabolites were sufficiently pure that their structures could be identified by spectral methods; for the radioactive metabolite R_f 0.68 (IV): ir (CCl_4), 3.0 (vs), 3.4 (w), 5.8 (w), 6.2 (s), 6.6 (s), 7.0 (s,) 7.3 (w), 7.9 (vs), 8.5 (w), 9.0 (vs) μ; nmr (CCl_4), δ 7.0 (multiplet), 6.6 (triplet) (combined area 7), 3.5 (singlet) (area 1), 0 (singlet) (area 14.5); mass spectrum ($\Sigma^{\%}_{101}$), *m/e* 105 (2), 107 (4), 135 (4), 151 (52), 152 (8), 153 (3), 166 (6), 167 (1), 180 (3); for synthetic *p*-trimethylsilylphenol: ir (CCl_4), 3.0 (vs), 3.4 (w), 6.3 (s), 6.7 (s), 7.1 (s), 7.4 (w), 8.0 (vs), 8.5 (w), 9.0 (vs) μ; nmr (CCl_4), δ 7.15, 7.04 (doublet), 6.34, 6.46, 6.56 (triplet) (combined area 1.0), 0 (area 2.3); mass spectrum ($\Sigma^{\%}_{100}$), 105 (2), 107 (3), 135 (2), 151 (64), 152 (10), 153 (3), 166 (7), 167 (1), 168 (0.8).

Authentic samples of *o*- and *m*-trimethylsilylphenol were also available.[11] Comparison of the ir and nmr spectra of these two compounds with those of the metabolite R_f 0.68 showed that the metabolite was neither of these compounds. The differences between the three were particularly evident in the fine structure and symmetry of the aromatic region (δ 7–7.5) of the nmr spectra; spectral data for radioactive metabolite R_f 0.56 (III): ir (CCl_4), 2.9 (vs), 3.5 (w), 3.85 (s), 7.0 (s), 7.95 (s), 8.95 (s), 9.9 (s) μ; nmr (CCl_4), δ 6.96 (broad multiplet) (area 4.8), 3.15 (singlet) (area 2), 0 (singlet) (area 6); mass spectrum ($\Sigma^{\%}_{105}$), *m/e* 151 (3), 135 (52), 136 (8), 137 (3); spectral data for synthetic (hydroxymethyl)dimethylphenylsilane: ir (neat), 3.0 (s), 3.4 (w), 7.0 (s), 8.0 (vs), 9.0 (s), 10.0 (s) μ; nmr (CCl_4), δ 7.0 (broad multiplet) (area 5), 3.15 (singlet) (area 2), 0 (singlet) (area 6); mass spectrum ($\Sigma^{\%}_{105}$), *m/e* 151 (7), 135 (68), 136 (11), 137 (4); spectral data for radioactive material R_f 0.09: ir, no data, soluble only in H_2O; nmr (D_2O), δ 6.96 (singlet) (area 5.6), 3.2 (singlet) (area 2), 0 (singlet) (area 5.8); mass spectrum (direct probe) ($\Sigma^{\%}_{100}$), *m/e* 105 (8.5), 107 (4.5), 135 (53), 136 (8.5), 137 (5.5), 147 (13), 148 (2), 149 (2), 151 (7.5), 152 (2.3), 153 (1.2).

B. Phenyldimethylsilane (II).—A portion of ether concentrate was taken directly to the mass spectrometer. The remainder of the material was purified using preparative tlc and the "purified" material was analyzed using spectral methods. Since the composition of the metabolite changed upon "purification" both sets of spectral data are given and discussed in the text: mass spectrum of radioactive metabolite prior to tlc purification (VII): *m/e* ($\Sigma^{\%}_{100}$) 105 (4), 107 (7.5), 122 (3), 128 (3), 137 (36.5), 138 (5.8), 139 (3.5), 152 (10.8), 153 (3), 154 (2.5), 193 (10.5), 194 (3), 195 (2.5), 271 (7.5), 272 (3), 273 (1); mass spectrum of synthetic dimethylphenylsilanol: *m/e* ($\Sigma^{\%}_{100}$) 137 (95), 138 (10), 139 (4).

Isolation of the Metabolite.—An aliquot (0.255 μCi) of the ether concentrate was subjected to tlc (silica gel, ether). Two active components were observed: one at R_f 0.80 (0.23 μCi, 90% of the activity) and another near the origin. Preparative tlc was used to isolate the compounds. Attempts to identify the compound(s) giving rise to the spot near the origin were unsuccessful; spectra data for radioactive R_f 0.80 metabolite: ir (CCl_4), 3.45 (w), 7.0 (s), 8.0 (s), 9.0 (s), 9.5 (vs) μ; nmr (CCl_4), δ 7.0 (multiplet), 0 (singlet); mass spectrum ($\Sigma^{\%}_{50}$), *m/e* 89 (13), 105 (7), 107 (4), 121 (5), 122 (4), 123 (4), 128 (9), 135 (7), 163 (4), 165 (4), 179 (3), 193 (24), 194 (6), 125 (4), 271 (11), 272 (4), 273 (1); spectral data for synthetic diphenyltetramethyldisiloxane: ir (neat), 3.4 (w), 7.0 (s), 8.0 (vs), 8.95 (vs), 9.5 (vs) μ; nmr (CCl_4), δ 7.0 (multiplet), 0 (singlet); mass spectrum ($\Sigma^{\%}_{50}$), *m/e* 89 (15), 128 (70), 135 (7), 193 (30), 194 (7), 195 (4), 271 (15), 272 (4), 271 (1).

Antifertility Agents. IV. 2,3-Diphenylbenzo- and 5,6-Polymethylenebenzofurans, 1,2-Diphenylnaphthofurans, and Some Related Compounds[1a]

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Among 2-phenyl-3-(*p*-β-(-aminoalkoxy- and thioalkoxyphenyl)-5,6-substituted benzofurans, naphtho[2,1-*b*]furans, and some related compounds synthesized and tested, 1-(*p*-β-pyrrolidinoethoxyphenyl)-2-phenylnaphtho[2,1-*b*]furan (**26**) and 2-phenyl-3-(*p*-β-pyrrolidinoethoxyphenyl)-5,6-tetramethylenebenzofuran (**50**) were found to possess marked antiimplantation activity in rats. Extended biological studies have been carried out with **26** for its antifertility activity. 2,3-Bis(*p*-methoxyphenyl)-5,6-dimethylbenzofuran showed significant antiinflammatory activity.

The synthesis of some substituted 2,3-diphenylbenzofurans and the antifertility activity of 2-phenyl-3-(*p*-β-pyrrolidinoethoxyphenyl)-6-methoxybenzofuran[1b] were reported earlier. This led to a further exploration of this group of compounds for antifertility activity and a study of their structure–activity relationship. The results are reported in this communication.

2-Phenyl-3-(*p*-hydroxyphenyl)benzofurans (I)[2] were prepared by a modification of the method of Brown,

(1) (a) Communication No. 1381 from the Central Drug Research Institute, Lucknow. (b) P. K. Grover, H. P. S. Chawla, N. Anand, V. P. Kamboj, and A. B. Kar, *J. Med. Chem.*, **8**, 720 (1965); (c) A. B. Kar, V. P. Kamboj, and B. S. Setty, *Indian J. Exp. Biol.*, **5**, 80 (1967).

(2) Roman numerals refer to the type of compounds, while Arabic numerals refer to the specific compounds as they appear in Table I.