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Abstract

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Synthesis of Several New Types of Silicon-Containing Aminoketones, Amino Alcohols, and Their Esters

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As far as we know, until now not a single aminoketone or amino alcohol containing silicon has been described. In this connection, we set ourselves the goal of carrying out the synthesis of Si derivatives of certain amino alcohols, the subject of our systematic study. Such hypothetical aminosilico alcohols appeared interesting from many points of view and, in particular, from the point of view of their possible physiological functions, in which the role of the silicon atoms or, more precisely, of the radical containing it, was to be revealed.

The first compounds whose synthesis we undertook were *p*-siliconeopentyl derivatives of ketones of the type:

$$(\mathrm{CH_3})_3\mathrm{Si}-\mathrm{CH_2}-\quad \mathrm{C_6H_4}\quad -\mathrm{CO}-\mathrm{R}$$

$$\mathrm{I}-\mathrm{R}=\mathrm{CH_3};\qquad \mathrm{II}-\mathrm{R}=\mathrm{C_2H_5};\qquad \mathrm{III}-\mathrm{R}=\mathrm{CH}\begin{matrix}/\mathrm{CH_3}\\ \backslash\mathrm{CH_3}\end{matrix}$$

The choice of precisely these compounds was dictated by the presence in them of the electron-donor (1) n-$(\mathrm{CH_3})_3\mathrm{Si}-\mathrm{CH_2}$-grouping. Judging from literature data (2), a methylene bridge strengthened the Si-$\mathrm{C_{aryl}}$ bond, in whose absence this bond was much weaker. Ketones I, II, and III were obtained by acylation of trimethylbenzylsilane in the presence of $\mathrm{AlCl_3}$ or $\mathrm{ZnCl_2}$, according to a method described by A. D. Petrov et al. (2) and partially modified by us. Ketones II and III were synthesized for the first time. Then ketones I and II, by means of the Mannich reaction carried out with dimethylamine, piperidine, and morpholine, were converted into the corresponding hydrochlorides of β-aminoketones (IV-VIII), of the general formula:

$$n\text{-}(\mathrm{CH_3})_3\mathrm{SiCH_2}-\mathrm{C_6H_4}-\mathrm{CO}-\mathrm{CH}-\mathrm{CH_2}-\mathrm{N}\Big\langle$$

R′

Compound No.	IV	V	VI	VII	VIII
R′	H	CH_3	H	CH_3	CH_3
$-N\langle$	$N(CH_3)_2$	$N(CH_3)_2$	N(morpholine ring with O)	N(piperidine ring)	N(morpholine ring with O)

Applied for the first time to Si-containing ketones, this reaction proceeded without complications, giving the required aminoketones in high yields; their purification, however, was possible not in all cases and only at the cost of large losses. With ketone III, despite every variation of conditions, the Mannich reaction did not take place; this, however, should not be attributed solely to the presence of silicon in it, since it is known that ketones of analogous structure with a branched alkyl react sluggishly in the Mannich reaction (^{3}).

Further, the amino ketone hydrochlorides, by a Grignard reaction that proceeded quite smoothly, were converted into tertiary amino alcohols (IX—XIII).

$$n\text{-}(CH_3)_3SiCH_2-C_6H_4-C(OH)(C_2H_5)-CH(R')-CH_2-N\langle$$

Compound No.	IX	X	XI	XII	XIII
R'	H	H	CH_3	CH_3	CH_3
$N\langle$	$N(CH_3)_2$	piperidino	$N(CH_3)_2$	piperidino	morpholino

Two secondary amino alcohols (XIV—XV) were obtained by us by hydrogenation of the corresponding amino ketone hydrochlorides over Raney nickel. In the course of hydrogenation, along with the formation of amino alcohols, destruction of the amino ketones occurred, proceeding differently depending on their structure. n-Siliconeopentyl-β-dimethylaminopropiophenone (IV), like analogous ketones without silicon (^{3}), was deaminated and decomposed (by 30%) with liberation of n-siliconeopentylpropiophenone (II). Meanwhile, n-siliconeopentyl-β-dimethylaminoisobutyrophenone (V) was deaminomethylated, i.e., decomposed (by 14%) not to n-siliconeopentylisobutyrophenone (III), as should have occurred upon deamination, but to n-siliconeopentylpropiophenone (II) (the "reverse" Mannich reaction).

$$\begin{array}{l}
(CH_3)_3Si-CH_2-C_6H_4-CO-CH_2-CH_2N(CH_3)_2\cdot HCl \quad (IV) \\
(CH_3)_2N-CH_2-CH(CH_3)-CO-C_6H_4-CH_2Si(CH_3)_3\cdot HCl \quad (V) \\
\qquad\qquad\qquad\quad \downarrow \qquad \downarrow \\
(CH_3)_3Si-CH_2-C_6H_4-CO-CH_2-CH_3 \quad (II)
\end{array}$$

The 2,4-dinitrophenylhydrazones of ketone (II), obtained in both cases, showed no depression with an authentic sample. An analogous deaminomethylation effect was discovered quite recently by Riviere (4) under the action on β-amino ketones of an aqueous-alcoholic solution of hydrogen chloride or of amines.

The amino alcohol bases, under mild conditions, were acylated with phenoxyacetyl chloride, which led to phenoxyacetates (XVI—XIX)

$$n\text{-}(CH_3)_3SiCH_2C_6H_4-C(OCOCH_2OC_6H_5)(R'')-CH(R')-CH_2-N(CH_3)_2$$

Compound No.	XVI	XVII	XVIII	XIX
R'	H	CH_3	H	CH_3
R''	H	C_2H_5	C_2H_5	H

These esters are intended to be tested first of all as local anesthetics. Recently published patent data (5) indicate the anesthetic activity of some silicon-containing compounds.

Experimental Part*

***n*-Siliconeopentylacetophenone (I).** From trimethylbenzylsilane (6) and acetyl chloride in the presence only of freshly distilled aluminum chloride, at a temperature not above 15-20°, a very pure ketone (I) was obtained in 40% yield. B.p. 94-95° (1 mm), n_D^{20} 1.5260. After the liquid crystallized in the form of colorless crystals with m.p. 39-40.5°.

The 2,4-dinitrophenylhydrazone melted at 206-207°. (Literature data: b.p. 142-144° (15 mm), n_D 1.5268; m.p. of the 2,4-dinitrophenylhydrazone 207-208°.) Ketones II and III were obtained in an analogous manner.

***p*-Siliconeopentylpropiophenone (II).** Yield 43.4%. B.p. 114-117° (1.5 mm), n_D^{20} 1.5233, m.p. 32-33°.

Found %: C 70.87; 70.73; H 9.12; 9.22; Si 13.00; 12.79

$C_{13}H_{20}OSi$. Calculated %: C 70.90; H 9.10; Si 12.72

M.p. of the 2,4-dinitrophenylhydrazone 182-183° (from alcohol)

Found %: N 14.10; 13.92; Si 7.12; 7.00

$C_{19}H_{24}O_4N_4Si$. Calculated %: N 14.00; Si 7.00

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* G. Solovei took part in carrying out some of the experiments.

***p*-Siliconeopentylisobutyrophenone (III).** Yield 48.7%, b.p. 120–125° (1.5 mm), n_D^{20} 1.5170, m.p. 28–28.5°.

Found %:	C 72.06; 72.08; H 9.38; 9.44; Si 11.98; 12.06
$C_{14}H_{22}OSi$. Calculated %:	C 71.50; H 9.38; Si 11.92

M.p. of the 2,4-dinitrophenylhydrazone 119–120° (from alcohol).

Found %:	N 13.41; 13.57; Si 6.70; 6.87
$C_{20}H_{26}O_4NSi$. Calculated %:	N 13.51; Si 6.76

***p*-Siliconeopentyl-β-dimethylaminopropiophenone (IV).** A mixture of 7.9 g of *p*-siliconeopentylacetophenone (I), 3.53 g of dimethylamine hydrochloride, 1.77 g of paraformaldehyde, and several drops of conc. hydrochloric acid in 18 ml of anhydrous alcohol was heated for 4.5 hr. After removal of the solvent under slight vacuum, the residue was washed with petroleum ether and dried. This gave 10.6 g (92%) of the technical hydrochloride of aminoketone (IV), m.p. 146–149°.

Found %:	N 6.63; 6.80.
$C_{15}H_{26}ONClSi$. Calculated %:	N 4.68

The product contains a small amount of dimethylamine hydrochloride.

Under analogous conditions other aminoketones (V–VIII) were synthesized.

***p*-Siliconeopentyl-β-dimethylaminoisobutyrophenone (V).** Yield 70% (technical product), m.p. 122–125°.

Found %:	Cl 14.63; 14.83.
$C_{16}H_{28}ONClSi$. Calculated %:	Cl 11.30

1-(*p*-Siliconeopentylphenyl)-3-dimethylaminopropan-1-ol (XIV). 15.4 g (0.0515 g-mol) of the technical hydrochloride of aminoketone (IV) was hydrogenated in 100 ml of anhydrous alcohol in the presence of 6.0 g of skeletal nickel catalyst. After absorption of 0.052 g-mol of hydrogen, the catalyst was filtered off, the alcohol was distilled off, the residue was acidified with hydrochloric acid (1 : 1), and the neutral products were extracted with ether. The ether layer was dried, the ether was distilled off, and the residue was distilled. This gave 3.36 g (29.6%) of *p*-siliconeopentylpropiophenone (II), b.p. 131–135° (2 mm) and m.p. 32–33°. The 2,4-dinitrophenylhydrazone melted at 181–182° and gave no depression with an authentic sample. The aqueous layer was made alkaline, the separated base was extracted several times with ether, the extract was dried, the ether was distilled off, and the residue was distilled. This gave 3.1 g (22.8%)

of amino alcohol (XIV), b.p. 135–138° (1 mm), m.p. 46.5–48°. H_{act} number 0.99; calculated 1.0. The hydrochloride melted at 146–148° (from a mixture of anhydrous acetone and alcohol). A mixed sample with the hydrochloride of aminoketone (IV) melted at 122–128°.

Found %:	N 4.81; 4.64;	Cl 10.80; 11.61;	Si 9.58; 9.59
$C_{15}H_{28}ONClSi$. Calculated %:	N 4.65;	Cl 11.77;	Si 9.29

1-*p*-Siliconeopentylphenyl-(2-methyl-3-dimethylaminopropan-1-ol) (XV). 14.0 g (0.0447 g-mol) of the technical hydrochloride of aminoketone (V) was hydrogenated in 100 ml of anhydrous alcohol in the presence of 6 g of skeletal nickel catalyst. After absorption of 0.043 g-mol.

hydrogen and work-up of the reaction mixture described in the preceding experiment—1.35 g (13.7%) of *n*-siliconeopentylpropiophenone (II) was obtained from the neutral products, with b.p. 127–130° (2 mm) and m.p. 31–32°. The 2,4-dinitrophenylhydrazone melted at 182–183° and gave no depression with an authentic sample.

From the basic products, 6.2 g (52.6%, calculated on the hydrogen absorbed) of the amino alcohol XV was obtained. B.p. 141–145° (1 mm), m.p. 81–82°.

Found, %:	N 5.0; 4.95;	Si 9.84; 9.86.	Number H_{act} 0.85
$C_{16}H_{29}ONSi$. Calculated, %:	N 5.03;	Si 10.01.	Number H_{act} 1.0

The hydrochloride melted at 207–207.5° (from acetone).

Found, %:	N 4.63; 4.37;	Cl 11.03; 11.20
$C_{16}H_{30}ONClSi$. Calculated, %:	N 4.44;	Cl 11.23

1-Ethyl-1-(*n*-siliconeopentylphenyl)-3-dimethylaminopropan-1-ol (IX). To the Grignard reagent prepared from 16.9 g of ethyl bromide, 3.08 g of magnesium, and 30 ml of anhydrous ether, 10.6 g of the technical hydrochloride of aminoketone (IV) was added gradually, with cooling by an ice-salt bath and stirring for 40 min. Stirring was continued for 2 h, and on the following day, after brief heating, the reaction mixture was decomposed with ice and acidified with hydrochloric acid (1:1). The neutral products were extracted with ether; the aqueous layer was alkalized with ammonia and then with alkali, and the separated base was extracted repeatedly with ether. The ether was dried and distilled off, and the residue was distilled. 4.9 g (47.3%) of amino alcohol (IX) was obtained, with b.p. 144–147° (1 mm), m.p. 68.5–70°.

Found, %: N 4.84; 4.98; Si 9.48; 9.20. Number H_{act} 1.1
$C_{17}H_{31}ONSi$. Calculated, %: N 4.80; Si 9.50. Number H_{act} 1.0

The hydrochloride melted at 161.5–162.5° (from acetone).

Found, %: N 4.78; 4.46; Cl 10.68; 11.07
$C_{17}H_{32}ONClSi$. Calculated, %: N 4.25; Cl 10.80

The remaining tertiary amino alcohols (X–XIII) were obtained in an analogous manner.

Phenoxyacetate of 1-ethyl-1-(*n*-siliconeopentylphenyl)-3-dimethylaminopropan-1-ol (XVIII). To a solution of 1.3 g of amino alcohol (IX) in 3 ml of anhydrous benzene, with cooling, a solution of 1.24 g of phenoxyacetic acid chloride in 2 ml of benzene was gradually added. Heating was observed, and after 1 h the solution solidified into a paste-like mass. On the following day the mixture was washed with petroleum ether, and the resulting precipitate was dried in a vacuum desiccator. 1.9 g (93%) of technical hydrochloride of phenoxyacetate (XVIII) was obtained, with m.p. 121–128°. After two recrystallizations from a mixture of acetone and chloroform, 0.8 g (39%) of product with m.p. 146–147° was obtained. Colorless fine crystals, soluble in water and insoluble in ether.

Found, %: N 3.13; 3.11; Cl 7.42; 7.62; Si 5.99; 6.20
$C_{25}H_{38}O_3NClSi$. Calculated, %: N 3.02; Cl 7.66; Si 6.05

The phenoxyacetates (XVI, XVII, XIX) were obtained analogously.

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Note: Figure translations are in progress. See original paper for figures.