Notes

A Silicon Analog of a Sympathomimetic Amine[1]

RALPH J. FESSENDEN AND MARVIN D. COON

Department of Chemistry, San Jose State College, San Jose, California

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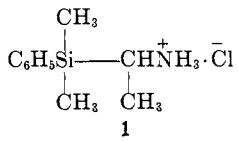
As the initial step in a program of the evaluation of the effect of a silicon atom as a substitute for a carbon atom in the skeletons of known active systems, we have prepared (α-aminoethyl)dimethylphenylsilane hydrochloride (**1**), which has a structure similar to that of some sympathomimetic amines. The direct carbon analog of **1**, compound **2**, has been studied previously[2] but was resynthesized in this work so that the two compounds could be compared under equivalent biological conditions.



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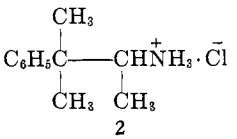

2

Because the silicon–carbon bond is longer than the carbon–carbon bond, **1** and **2** would be expected to differ subtly in geometry. At the same time, **1** and **2** would be expected to differ in their acidities due to the differences in electronegativity between carbon and silicon. The acidities of **1** and **2** were measured and indeed the pK_a of **1** was found to be 10.26 while that of **2** was 9.73.

It is significant that preliminary pharmacological evaluation reveals no gross difference in the activity of **1** and **2**. The toxicities of **1** and **2** appear to be equivalent: **1**, LD_{50}, 105–113 mg./kg. (0.49–0.51 mmole/kg.); **2**, LD_{50}, 102–107 mg./kg. (0.51–0.53 mmole/kg.). The ECG and EEG show qualitative similarities. At toxic doses, neither compound showed analeptic activity on anesthesized rats (sodium pentobarbital), but both did induce an increase in the depth and the rate of respiration.

Experimental[3]

(α-Chloroethyl)dichlorophenylsilane.—To a solution of 793 g. (4.0 moles) of (α-chloroethyl)trichlorosilane[4] in 750 ml. of ether was added, over a period of 2 hr., 4.0 moles of phenylmagnesium bromide. The mixture was refluxed for 12 hr., then suction filtered using Filter-Cel. The filtrate was concentrated by distillation at atmospheric pressure, then refiltered. Fractional distillation yielded 534 g. (56%) of product, b.p. 142° (26 mm.), $n^{25}D$ 1.5383.

Anal. Calcd. for $C_8H_9Cl_3Si$: C, 40.08; H, 3.76. Found: C, 39.71; H, 3.77.

(α-Chloroethyl)dimethylphenylsilane.—To 930 ml. (2.7 moles) of commercial 3 *M* methylmagnesium bromide was added, over a period of 40 min. with cooling, 290 g. (1.2 moles) of (α-chloroethyl)dichlorophenylsilane. After the addition had been completed, the mixture was heated at reflux for 24 hr. Water work-up, followed by fractional distillation, yielded 177.2 g. (71%) of material of b.p. 90–97° (4 mm.), $n^{24}D$ 1.5200. An analytical sample was obtained with a silicone preparative g.l.p.c. column.

Anal. Calcd. for $C_{10}H_{15}ClSi$: C, 60.0; H, 7.62. Found: C, 60.50; H, 7.27.

(α-Iodoethyl)dimethylphenylsilane.—A mixture of 60.2 g. (0.30 mole) of (α-chloroethyl)dimethylphenylsilane, 120 g. (0.30 mole) of sodium iodide, and 300 ml. of acetone was heated at reflux for 11 days. The mixture was concentrated by distillation then worked up with water. Fractional distillation yielded 68.3 g. (78%) of an oil, b.p. 130° (10 mm.), $n^{23}D$ 1.5700.

Anal. Calcd. for $C_{10}H_{15}ISi$: C, 41.38; H, 5.21; I, 43.73. Found: C, 41.22; H, 5.07; I, 43.38.

(α-Aminoethyl)dimethylphenylsilane Hydrochloride.—In a sealed bomb were placed 16.6 g. (0.057 mole) of (α-iodoethyl)-dimethylphenylsilane and *ca.* 75 ml. of liquid ammonia. The mixture was heated at 165° for 3.5 hr. After the excess ammonia was allowed to escape, the residue was transferred to a flask, made strongly basic with 6 *N* sodium hydroxide solution, and then extracted with ether. Upon distillation of the ethereal extract, 5.2 g. (51%) of the free amine, b.p. 90–103° (2.0 mm.), $n^{22}D$ 1.5178, was obtained. The yield varied from 23 to 62% using equivalent reaction conditions.

To 8.6 g. of the free amine was added 75 ml. of water. Then 6 *N* hydrochloric acid was added dropwise until the amine dissolved. The pH of the solution was readjusted to 7.0 by the addition of sodium bicarbonate solution. The excess water was evaporated using a hot plate until white fumes were noted. The liquid (*ca.* 20 ml.) was chilled and the resultant solid was filtered. Recrystallization from methanol–acetone yielded 7.1 g. (69%) of the hydrochloride, m.p. 192.5–193°.

Anal. Calcd. for $C_{10}H_{18}ClNS$: C, 55.68; H, 8.35; Cl, 16.47; Si, 12.99. Found: C, 55.60; H, 8.18; Cl, 16.68; Si, 13.05.

2-Amino-3-methyl-3-phenylbutane Hydrochloride.—The procedure of Suter and Weston[2] was employed. Reaction of phenylacetone and methyl iodide in the presence of sodium isopropoxide gave a 37% yield of 1-methyl-1-phenyl-2-propanone, b.p. 88° (8 mm.), $n^{26}D$ 1.5089. Dimethylation was carried out using methyl iodide and potassium *t*-butoxide. Gas phase chromatographic analysis of the distillation fractions boiling at 83–89° (8 mm.), $n^{27}D$ 1.5179–1.5089, showed, besides the starting monomethylated material, two other components. After repeated distillation, the higher boiling material was isolated, b.p. 89° (8 mm.), $n^{27}D$ 1.5089. N.m.r. analysis of this material, in agreement with the assigned structure, showed singlets at δ 1.40, 1.80, and 7.05. The ketone was converted to the amine hydrochloride using the procedure described by Suter and Weston in 64% yield, m.p. 217–219° (lit.[2] m.p. 213.5–215°).

Pharmacological Studies.—The toxicity of **2** has been reported by Suter and Weston as 160 mg./kg. using oral administration and female mice. In the present work Webster Swiss white mice, 15–20 g., were used. The amine hydrochloride was introduced intraperitoneally in a phosphate (0.01 *M*) buffered solution (pH 7.4). Death occurred within 15 min. of injection. The absolute values of the toxic doses varied from day to day. The values reported were obtained from injections administered within a given 4-hr. period using 50 mice per compound within the dosage range of 90 mg./kg. to 130 mg./kg. and using 10 mice per level. The ECG and EEG studies were carried out with rats (Sprague–Dawley, 300–400 g., sodium pentobarbital sedation) with both compounds at equivalent doses. No analeptic activity was noted. Rate and depth of respiration increased initially, followed by death from respiratory failure. Mice given nonlethal doses of either compound exhibited intense excitement.

Acidity Measurements.—The pK_a of each compound was

(1) This work was supported by a grant (GM 10122) from the National Institutes of Health, U. S. Public Health Service.

(2) C. M. Suter and A. W. Weston, *J. Am. Chem. Soc.*, **64**, 533 (1942).

(3) All melting points are corrected and were obtained using a Fischer-Johns melting point apparatus. Distillations were accomplished using an 85-cm. modified Podbielniak column (*cf.* J. Cason and H. Rapoport, "Laboratory Text in Organic Chemistry," Prentice-Hall, Inc., Englewood Cliffs, N. J., 1962, p. 289). Microanalyses were performed by the Berkeley Analytical Laboratory, Berkeley, Calif. The n.m.r. spectrum was obtained using a Varian A-60 instrument and was run in 15-wt. % carbon tetrachloride solution using tetramethylsilane as an internal reference.

(4) L. H. Sommer and F. C. Whitmore, *J. Am. Chem. Soc.*, **68**, 485 (1946).

measured using the potentiometric method, titrating the amine hydrochloride with sodium hydroxide. The value for **1** is based upon 55 points distributed among three concentrations with an average deviation of 0.039 pK_a units. For **2**, 54 points distributed among three concentrations were used. The average deviation was 0.043 pK_a units.

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Cyclopropane Analogs of Choline Ethers[1]

ALFRED BURGER AND HANS-JØRGEN PETERSEN

Department of Chemistry, University of Virginia, Charlottesville, Virginia

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Although many esters and ethers of choline have been examined for their activity in cholinergic and cholinesterase systems, the effect of conformational changes of the –O–C–C–N segment has not yet been defined. A transition from cisoid to transoid shapes has been considered as a possible source of the stimulatory and depressant components of such compounds.[2] Branching of the carbon chain with small alkyl groups greatly prolongs the activities, probably by steric interference with the reactions of the respective compounds at biocatalytical sites.[3] In such branched compounds, marked differences in the activities of optical isomers and diastereoisomers have been observed.[4] We are now recording the synthesis and biological evaluation of some 2-N-alkoxycyclopropyl-N,N,N-trimethylammonium salts in which the methyl group of the α- and β-methylcholine ethers, or the methylene group of the muscarinic agent, (2-methoxyallyl)trimethylammonium hydroxide[5] have been incorporated in a small rigid ring. In the case of N-(2-benzyloxycyclopropyl)-N,N,N-trimethylammonium iodides, both the *cis* and *trans* forms have been isolated and tested.

These compounds were synthesized by subjecting the corresponding 2-alkoxycyclopropanecarboxylic acids to modified Curtius degradations and quaternizing the respective 2-alkoxycyclopropylamines with methyl iodide. During the Curtius procedures, the azides were rearranged either to the isocyanates, or better, transformed to the corresponding benzyl carbamates; the latter could be hydrolyzed or hydrogenolyzed to the amines.

The configurations assigned to the N-(2-benzyloxycyclopropyl)-N,N,N-trimethylammonium iodides are supported by the n.m.r. spectra of these salts (see Table I). In the *trans* isomer, the positive nitrogen may be expected to cause a larger shift of the proton peak in the 2-position due to its higher shielding effect. Furthermore, the peak of the benzyl α-protons should be shifted less in the case of the *trans* isomer. As shown in the Experimental section, the *trans* isomer predominates in the reaction mixture.

TABLE I

NUCLEAR MAGNETIC RESONANCE SPECTRA OF *cis*- AND *trans*-N-(2-BENZYLOXYCYCLOPROPYL)-N,N,N-TRIMETHYLAMMONIUM IODIDES IN DEUTERATED DIMETHYL SULFOXIDE[a]

cis isomer,[b] τ-values	*trans* isomer,[c] τ-values	
2.54	2.57	5 Phenyl protons
5.29	5.35	2 Benzyl protons
6.3–6.7	5.74	1 Proton at 2-position of cyclopropane ring; blurred for *cis* by the solvent peak
6.76	6.89	9 N-CH_3 protons
8.3–9.1	8.2–9.0	CH_2 protons of 3-position in cyclopropane ring

[a] Tetramethylsilane as the internal standard. [b] More soluble; m.p. 164–168° dec. [c] Less soluble; m.p. 168.5–169°.

Arguments supporting the *trans* configuration of the only isomer isolated in the case of N-(2-butoxycyclopropyl)-N,N,N-trimethylammonium iodide are presented in the Experimental section.

Pharmacology.—The methodology for tests with *cis*-2-N-benzyloxycyclopropyl-N,N,N-trimethylammonium iodide (I), the *trans* isomer (II), and *trans*-N-(2-*n*-butoxycyclopropyl)-N,N,N-trimethylammonium iodide (III) is summarized in the Experimental section.[6] On the isolated ileum of the guinea pig, I had no cholinergic activity up to 10^{-2} mg./ml. At $1–2 \times 10^{-3}$ mg./ml. it reduced acetylcholine-caused contractions by 50%. At 10^{-2} mg./ml. II showed neither a cholinergic nor anticholinergic action, while III at 5×10^{-3}–2.5×10^{-2} mg./ml. led to contractions of short duration. This compares with a similar effect of acetylcholine at 2.5×10^{-6} mg./ml. In contrast to acetylcholine, the effect of III was not cancelled by atropine but was abolished by 10^{-3} mg./ml. of hexamethonium.

At 0.25 mg./kg., I raised the blood pressure briefly in the anesthetized cat; a rise of 60 mm. occurred after 0.5 mg./kg., but after 1 mg./kg. it amounted to only 30 mm., and could no longer be demonstrated after 2 mg./kg. The pressor effect was not affected by hexamethonium, but was greatly decreased by 1 mg./kg. of phentolamine. By contrast, the *trans* isomer (II) caused no effect up to 1 mg./kg., and 5 mg./kg. led to an acute drop in pressure with full recovery within 5 min. Compound III (0.1 mg./kg.) produced a strong pressor effect of short duration which could be decreased moderately by atropine. Phentolamine or hexamethonium greatly decreased the pressor effect of large doses of III, and abolished it after low doses. A combination of the two agents always cancelled the pressor effect. Pretreatment with reserpine (see Experimental section) decreased the pressor action of III; a clear pressor effect was achieved with 0.5

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(2) H. Sörum, *Acta Chem. Scand.*, **13**, 345 (1959).

(3) For a review see M. E. Wolff in "Medicinal Chemistry," A. Burger Ed., Interscience Publishers, Inc., New York, N. Y., 1961, p. 424.

(4) A. H. Beckett, N. J. Harper, and J. W. Clitherow, *J. Pharm. Pharmacol.*, **15**, 349, 362 (1963); P. G. Waser, *Pharmacol. Rev.*, **13**, 465 (1961).

(5) G. J. Hecht, *Klin. Wochschr.*, **14**, 957 (1935).

(6) We are grateful to Dr. H. H. Frey, Leo Pharmaceutical Products, Ballerup, Denmark, for these data.