SUBSTITUTED PYRIDINES

1,2,5-TRIMETHYL-4-TRIPHENYLSILYL-4-PIPERIDOL AND 2,5-DIMETHYL-4-TRIPHENYLSILYLPYRIDINE

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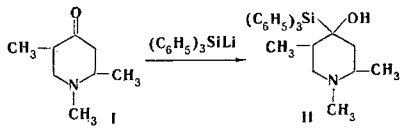
1,2,5-Trimethyl-4-triphenylsilyl-4-piperidol was obtained and converted to 2,5-dimethyl-4-triphenylsilylpyridine. Several transformations of the isomeric piperidols isolated and of the substituted pyridines were examined.

Triphenylsylalkylcarbinols are formed by the reaction of triphenylsilyllithium with aliphatic ketones [1,2], while triphenylbenzhydrylhydroxysilane is obtained by the reaction of triphenylsilyllithium with benzophenone [3]. The silane apparently forms as a result of isomerization of the normal product of addition of the organometallic compound to the carbonyl group.

In order to study the possibility of the synthesis of the potentially physiologically active organosilicon compounds of piperidine derivatives we have studied the reaction of triphenylsilyllithium with 1,2,5-trimethyl-4-piperidine (1) in tetrahydrofuran.



Four diastereoisomeric forms are theoretically possible for piperidol II, each of which can be represented by means of several conformations. Diastereoisomers II are, of course, not equivalent in a thermodynamic respect, and it is possible that not all of them are formed during their synthesis.

We isolated two diastereoisomers of II from the reaction products by successive crystallization: the γ isomer with mp 99.5-100.1 deg C and R_f 0.278, and the α isomer with mp 153-154.5 deg and R_f 0.078. The desigations (γ and α) of the diastereoisomers of II were given on the basis of a comparison of their chromatographic mobilities with the isomeric γ- and α-1,2,5-trimethyl-4-phenyl-4-piperidols [4,5]. These tertiary alcohols do not form urethanes with phenyl isocyanate. The presence of an OH group in diastereoisomeric piperidols II was demonstrated analytically and by means of the IR spectra (the γ isomer has a band for the valence vibrations of the OH group with a maximum at 3419 cm^{-1}, while the α isomer has a band at 3130 cm^{-1}). Both of these isomers are apparently related to the derivatives of piperidone I with the most thermodynamically favorable trans-equatorial position of the methyl groups attached to the C_2 and C_5 atoms. The predominant formation of tertiary piperidols of precisely this configuration was established from rather extensive experimental data [6]. It might have been assumed that, because of steric hindrance created by the methyl group attached to C_5, attack by the bulky triphenylsilyl radical on the carbonyl group in the direction in which an isomer with the cis orientation of this radical and the C_5 methyl group should be formed would be unlikely. However, this hindrance is not so significant, apparently because of the large volume of the silicon atom.

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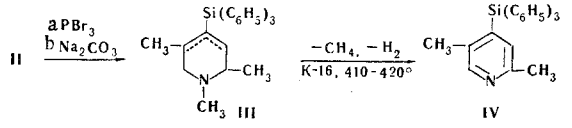
The yield of piperidol II depends to a significant degree on the method used for its isolation. If II is isolated by means of vacuum distillation rather than crystallization of the reaction products the yield decreases sharply; the decrease in yield is greater, the higher the still temperature during distillation. Thus, for example, the yield was ~3.5% when the still temperature was 300-320 deg, and only the γ isomer of II was isolated. An investigation of the thermal stability of the individual isomers of II indicated that they undergo profound transformations at high temperatures. The γ isomer is more thermally stable than the α isomer. The γ isomer remains unchanged if it is kept at 200 deg for 12 h, but at 300 deg (8 h) it is completely transformed. The α isomer undergoes complete transformation even at 190-195 deg (14 h). The transformation of the α isomer apparently proceeds unambigously on heating. In the process, only one substance is formed, to which the 1,2,5-trimethyl-4-triphenylsiloxypiperidine structure can be assigned on the basis of the analytical characteristics and the IR spectrum (intense band at 1097 cm^{-1}, which is ascribed to the valence vibrations of the Si—O bond of the Si—O—C group). The transformation which the α isomer of piperidol II undergoes at high temperatures is therefore analogous to the isomerization of triorganosilylcarbinols (which contain a hydroxyl group in the α-position with respect to silicon) to the corresponding siloxy derivatives [7].

In the case of the γ isomer of II, the transformation at high temperatures is more complex. Dehydration of piperidol II apparently occurs in addition to the analogous isomerization of $Ph_3Si \rightarrow O$, and hydrolysis of the siloxy derivatives occurs in the presence of the water evolved in the process. According to the chromatographic analytical data, four different substances are formed during the thermal transformations of the γ isomer. It must be noted that the substances obtained during a study of the thermolysis of the individual isomers of II were also obtained from the reaction products when vacuum distillation was used for the isolation of II.

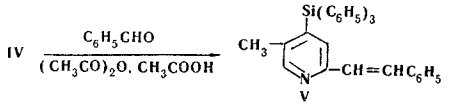
Piperidol II was dehydrated with phosphorus tribromide in benzene with subsequent treatment with sodium carbonate. A mixture of isomeric 1,2,5-trimethyl-4-triphenylsilylpiperideines (III) (isomers with respect to the position of the double bond in the piperidine ring) was obtained in 65% yield from the mixture of diastereoisomers II.

Under the same conditions, the dehydration of the γ isomer of II proceeds stereospecifically with the formation of only one piperidine (III) (with mp 94-96 deg). The absorption band at 1624-1634 cm^{-1} in the IR spectra of II is ascribed to the valence vibrations of the double bond. II could not be dehydrated with either concentrated hydrochloric acid or phosphorus pentoxide.



To synthesize 2,5-dimethyl-4-triphenylsilypyridine (IV), piperideine III was dehydrated and N-demethylated with a K-16 industrial catalyst at 410-420 deg. Substituted pyridine base IV was obtained in 61% yield. 2,5-Dimethyl-4-triphenylsilpyridine is a colorless, crystalline substance (mp 157-158 deg) that is soluble in acetone, alcohols, ether, and ligroin. It is not altered by refluxing with an aqueous alcohol solutions of perchloric acid.

A stilbazole — 5-methyl-4-triphenylsilyl-2-styrylpyridine (V) — is obtained by the condensation of IV with benzaldehyde. The absorption band at 1642 cm^{-1} in the IR spectrum of V is ascribed to the valence vibrations of the double bond.



The IR spectra of all of the compounds obtained have a band at 1100 cm^{-1}, which indicates [2] the presence of a triphenylsilyl grouping in molecules of these compounds.

EXPERIMENTAL

Thin-layer chromatography of the compounds was carried out using a mixture of equal amounts of activity II and activity III aluminum oxides and a hexane-ethyl acetate (3 : 1) system.

1,2,5-Trimethyl-4-triphenylsilyl-4-piperidol (II). A. A solution of 73.5 g (0.25 mole) of triphenylchlorosilane in 470 ml of tetrahydrofuran (freshly distilled over lithium aluminum hydride) was added to 7.5 g (1.09 g-atom) of finely cut lithium at 0 deg in the course of 2.5 h. The mixture was then stirred for 4 h at room temperature, The greenish-brown solution of triphenylsilyllithium was filtered, and 106 g (0.75 mole) of piperidone I in 200 ml of tetrahydrofuran was added in the course of 2 h to the filtrate at 0 deg. The mixture was then stirred for 1 h at room temperature. All of the operations were carried out under nitrogen. The mixture was treated with 18% hydrochloric acid until it gave an acid reaction to Congo red. The solvent was then removed by distillation, and the residue was treated with ether (four 150-ml portions). The residue of salts of the organic bases was treated with a saturated aqueous solution of potassium hydroxide. The organic bases were extracted with ether (five 200-ml portions). The ether extract after removal of 74.71 g (0.53 mole) of starting I by distillation yielded 64.9 g of a glassy residue which was crystallized from 75 ml of absolute ethanol to give 41.4 g (41.3%) if crystals with mp 62-78 deg (from hexane). According to thin-layer chromatography the crystals are a mixture of two substances (R_f 0.278 and 0.078). Stepwise crystallization from ethanol-hexane yielded 32.8 g of the γ isomer of piperidol II with mp 99.5-100.1 deg (from hexane) with R_f 0.278. Found %: C 77.73; H 7.66; N 3.24; OH 3.99. $C_{26}H_{31}NOSi$. Calc. %: C 77.77; H 7.73; N 3.49; OH 4.23. The picrate had mp 209.5-210 deg (from alcohol). Found %: N 8.64. $C_{26}H_{31}NOSi \cdot C_6H_3N_3O_7$. Cal. %: N 8.88.

The mother liquor remaining after isolation of the γ isomer was evaporated. Cooling of the condensate yielded 4.1 g of the α isomer of II with mp 153-154.5 deg (from ligroin) and R_f 0.078. Found %: C 77.79; H 8.07; N 3.30; OH 4.60. $C_{26}H_{31}NOSi$. Calc. %: C 77.77; H 7.73; N 3.49; OH 4.23. The picrate had mp 205-206 deg (from alcohol–acetone). Found %: N 8.68. $C_{26}H_{31}NOSi \cdot C_6H_3N_3O_7$. Calc. %: N 8.88.

The ether extract of the neutral reaction products yielded 16.2 g of a mixture of silicon-containing substances. Hexaphenyldisiloxane (mp 224-226 deg) and triphenylsilanol (mp 151-152 deg) were isolated from then by fractional crystallization.

B. The following reagents and quantities were taken for a similar synthesis: 58.8 g (0.2 mole) of triphenylchlorosilane, 6 g (0.9 g-atom) of lithium, 56.4 g (0.4 mole) of piperidine I, and 680 ml of tetrahydrofuran. After the completion of the synthesis, the mixture was held at room temperature for 10 h. Water (250 ml) was then added with cooling and vigorous stirring. The upper layer was separated, and the tetrahydrofuran was distilled from it under a slight vacuum. The residue was added to the aqueous layer. It was then treated with 18% hydrochloric acid until it was acid to Congo red. The neutral substances were extracted with ether (three 200-ml portions). The ether extract yielded 19.34 g of a mixture of substances from which tetraphenylsilane (mp 230-232 deg) and triphenylsilanol (mp 149-151 deg) were isolated.

Potassium hydroxide (85 g) was added to a solution of the salts of the organic bases. The bases were extracted with ether (five 150-ml portions). The residue (50.7 g) after removal of the ether was a transparent viscous mass; 38.5 g of this residue was vacuum distilled to give 4.1 g of a mixture (according to thin-layer chromatography) of starting piperidone I and 1,2,5-trimethyl-4-piperidol [bp 65-97 deg (4 mm)] 17 g of a fraction with bp 235-247 deg (4 mm), and 14.5 g of undistilled residue (an orange, transparent, glassy mass). Successive crystallization of the second fraction from petroleum ether and then from ethanol yielded 8.22 g [0.02 mole (13.5%)] of the γ isomer of II with mp 98.5-100.1 deg and R_f 0.0278. According to thin-layer chromatography, the mother liquor remaining after isolation of piperidol II contained no less than four substances but did not contain the α isomer of II.

C. The α isomer of II (0.15 g) was heated in an evacuated ampule at 190-195 deg for 14 h. According to chromatographic analysis, the reaction products contained only one substance (R_f 0.625) which differed from the starting piperidol (R_f 0.078). The analytical data on the picrate obtained from it (mp 147-148 deg, from alcohol corresponded to 1,2,5-trimethyl-4-triphenylsiloxypiperidine. Found %: N 8.87. $C_{26}H_{31}NOSi \cdot C_6H_3N_3O_7$. Calc. %: N 8.88.

A mixture of picrates, from which a picrate with mp 146-148 deg (from alcohol) was isolated by fractional crystallization and did not give a melting-point depression when mixed with the above indicated sample, was obtained from the bases contained in the mother liquor remaining after isolation of the γ isomer of piperidol II [see (B)]. The base isolated from the picrate with mp 146-148 deg was chromatographically identical (R_f 0.625) to the base obtained by isomerization of the α isomer of II.

D. The γ isomer of piperidol II (0.2 g) was heated under similar conditions at 290-300 deg for 23 h. According to chromatographic analysis, the reaction products contained four substances. The first of these had R_f 0.105, while the second (major component) had R'_f 0.455; the base isolated from the picrate (mp 161-162.8 deg, from alcohol), which was obtained by fractional crystallization of the mixture of picrates [see (C)], had a similar chromatographic mobility. According to the analytical data, one of the isomers of 1,2,5-trimethyl-4-triphenylsiloxypiperidine corresponds to this base. Found %: N 3.40. $C_{26}H_{31}NOSi$. Calc. %: N 3.49. Picrate. Found %: N 8.60. $C_{26}H_{31}NOSi \cdot C_6H_3N_3O_7$. Calc. %: N 8.88. The third substance had R''_f 0.605, while the fourth substance had R'''_f 0.693.

1,2,5-Trimethyl-4-triphenylsilpiperidine (III). A. A mixture of 4.1 g (0.0102 mole) of the γ isomer of piperidol II and 3.7 g (0.0137 mole) of phosphorus tribromide was refluxed in 50 ml of benzene for 24 h. The mixture was neutralized with aqueous sodium carbonate (excess) and refluxed for 1 h. The benzene solution was separated and the organic bases were extracted with ether. The combined extracts yielded 3.2 g of a residue which was crystallized from hexane to give 1.5 g (0.004 mole) of 1,2,5-trimethyl-4-triphenylsilylpiperidine III with mp 94-96 deg and R_f 0.516. Found %: C 81.44; H 7.70; N 3.39. $C_{26}H_{29}NSi$. Calc. %: C 81.32; H 7.56; N 3.66. The picrate had mp 169-172 deg (from alcohol). Found %: N 9.19. $C_{26}H_{29}NSi \cdot C_6H_3N_3O_7$. Calc. %: 9.15.

B. A solution of 17.3 g (0.043 mole) of a mixture of isomers of piperidol II in 200 ml of benzene was refluxed for 20 h with 18.5 g of phosphorus tribromide. A solution of 48 g of sodium carbonate in 150 ml of water was then added. After vigorous stirring for 1 h, the benzene solution was separated, and the organic bases were extracted from the aqueous layer with ether. The combined benzene and ether extracts yielded 13.8 g of a residue which was crystallized from hexane to give a mixture of isomers of III with mp 81-85 deg and R_f 0.515 and 0.745. Found %: C 81.36; H 7.46; N 3.43. $C_{26}H_{29}NSi$. Calc. %: C 81.32; H 7.56; N 3.66. The picrate had mp 163-169 deg (from alcohol). Found %; N 9.40. $C_{26}H_{29}NSi \cdot C_6H_3N_3O_7$. Calc. %: N 9.15

2,5-Dimethyl-4-trimethylsilylpyridine (IV). Dehydration and N-demethylation of III were carried out in a flow system. The catalyst (100 ml) was K-16, and the temperature in the catalyst zone was 410-420 deg. A solution of 8.14 g of III and 25 ml of benzene was passed at a constant rate for 2 h through the catalysis tube. A total of 0.7 liter of gas was collected (18.5 deg, 754 mm, 60.6% CH_4, 39.6% H_2, traces of C_2H_6). The catalyzate yielded 4.72 g (61%) of crystals. Crystallization of these crystals from ligroin yielded 3.4 g of substituted pyridine IV with mp 157-158 deg and R_f 0.625. Found %: C 82.34; H 6.36; N 3.68. $C_{25}H_{23}NSi$. Calc. %: C 82.30; H 6.31; N 3.84. The picrate had mp 178-179 deg (from alcohol). Found %: N 9.45 $C_{25}H_{23}NSi \cdot C_6H_3N_3O_7$. Calc. %: N 9.43.

5-Methyl-4-triphenylsilyl-2-styrylpyridine (V). A mixture of 1.18 g (0.0032 mole) of IV, 0.7 g (0.0069 mole) of benzaldehyde, 0.6 g of acetic anhydride, and 0.3 g of acetic acid was refluxed for 22 h. The excess benzaldehyde, acetic anhydride, and acetic acid were then removed by vacuum distillation. The dark-brown residue was treated with 18% hydrochloric acid until it gave an acid reaction to Congo red. The neutral reaction products were extracted with ether. The residue of the salts of the organic bases was treated with a saturated solution of aqueous potassium hydroxide. The organic bases were extracted with ether. The residue (0.69 g) after removal of the ether was passed through a column (1.6 × 10 cm) filled with activity II aluminum oxide (with ligroin as the elluant) to give 0.47 g (0.001 mole) of V with 166.5-168 deg (from hexane-ligroin) and R_f 0.725. Found %: C 84.92; H 6.07; N 3.07. $C_{32}H_{27}NSi$. Calc. %: 84.70; H 5.95; N 3.09. Also isolated was 0.14 g of a mixture (according to thin-layer chromatography) of IV and V. The picrate of V had mp > 237 deg (from acetone). Found %: N 8.02. $C_{32}H_{27}NSi \cdot C_6H_3N_3O_7$. Calc. %: N 8.20.

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