SYNTHESIS AND THREE-DIMENSIONAL STRUCTURES OF SUBSTITUTED 4-SILYL-4-PIPERIDOLS

N. S. Prostakov, A. V. Varlamov,
V. P. Zvolinskii, G. I. Cherenkova,
Butros Musa Butros, and Maria Elena Sintra

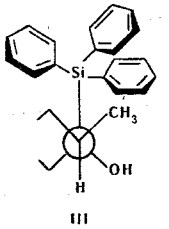
UDC 547.823'245.07:541.63

1,2 5-Trimethyl-4-(methyldiphenylsilyl)- and 4-(dimethylphenyl)silyl-4-piperidols were obtained. The isomers of these piperidols of the γ series, which exist in the chair conformation, have all of their substituents, except the hydroxyl group, equatorially oriented. The isomers of the α series exist in solution in the form of an equilibrium mixture of chair and boat conformations, and all of the substituents, except the silyl grouping, are equatorially oriented in the chair conformation.

Continuing our research on the synthesis and study of tertiary 4-piperidols and their derivatives (including the effective analgetics, the isomeric prodines and promedols), we turned to the preparation of 1,2,5-trimethyl-4-(methyldiphenylsilyl)- and 4-(dimethylphenylsilyl)-4-piperidols (I, II), which were synthesized by a method similar to that described previously for the preparation of 1,2,5-trimethyl-4-triphenylsilyl-4-piperidol (III) from 1,2,5-trimethyl-4-piperidone [1]. In the present communication we examine the three-dimensional structures of these piperidols.

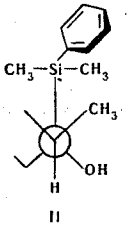
Piperidols I and III were isolated in the form of two isomers. It was established preparatively and chromatographically that piperidol II is present in the form of a single isomer. Analysis of the spectral characteristics of piperidols I-III and the fact that the starting 1,2,5-trimethyl-4-piperidone has primarily a trans-diequatorial orientation of the 2- and 5-CH_3 groups [2, 3] provide evidence that the same orientation of the methyl groups is retained for piperidols I-III. The assumption of the orientation of the substituents attached to C_4 in isomers of the piperidols obtained in this study was made on the basis of a comparison of their chromatographic mobilities. The alcohols with higher chromatographic mobilities (with an axial hydroxyl group) were designated the γ isomers, and those with lower chromatographic mobilities (with an equatorial hydroxyl group) were designated the α isomers; these designations were made in analogy with the isomeric 1,2 5-trimethyl-4-phenyl-4-piperidols [4].

The absence of the α isomer of piperidol II and the different $\gamma:\alpha$ isomer ratios for piperidols III and I (9:1 and 1:0.02, respectively) are apparently explained by steric factors due to interaction of the substituents attached to the silicon atom with the 5-CH_3 group. These iterations are expressed to a lesser extent in the case of the triphenylsilyl substituent because the phenyl rings may be located in planes in which their interaction with the 5-CH_3 group is excluded, but these interactions turn out to be of considerable magnitude in the case of the dimethylphenylsilyl substituent (interaction of the methyl groups).



III

α isomer



II

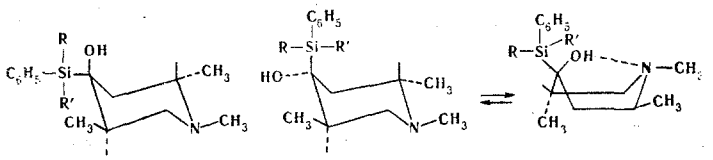
α isomer (not formed)

Patrice Lumumba International-Friendship University, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 502-505, April, 1976. Original article submitted May 15, 1975.

It follows from an examination of the Stuart–Briegleb models of the possible isomers of II that in the case of an axial orientation of the dimethylphenylsilyl grouping there may be only two hindered positions at which ring deformation occurs and strong steric interaction of the methyl groups attached to the silicon atom and C_5 develops.

It follows from the data from the IR spectra (presented in the experimental section) of the γ and α isomers of piperidols I and III that in the crystalline state they exist in an associated state in which the equatorial hydroxyl groups of the α isomers are more accessible for the formation of intermolecular OH...N hydrogen bonds. On the basis of the fact that the band of a bonded hydroxyl group vanishes completely in the IR spectra of even saturated solutions of the γ isomers of I and III in carbon tetrachloride and a band corresponding to a free hydroxyl group appears in the spectra, it can be assumed that these isomers exist in the chair conformation. However, the spectra of solutions of the α isomers contain bands of both bonded and free hydroxyl groups, and the intensity of the latter band does not change on dilution in the case of III. Consequently, a chair$\rightleftharpoons$boat equilibrium conformational system exists in solutions of the α isomers of these piperidols. The higher frequency of the free hydroxyl group of the γ isomers as compared with the same frequency for the corresponding α isomers indicates an axial orientation of the hydroxyl groups in the γ isomers and an equatorial orientation in the α isomer [5, 6]. This conclusion is confirmed by the experimentally determined dipole moments of the α isomer (2.3 ± 0.05 D) and the γ isomer (1.6 ± 0.1 D) of III (the determining factor is the vector moment of the OH and $N=CH_3$ groups [7, 8]. The fact that the ν_{C-O} and δ_{OH} bands in the spectra of the γ isomers (axial OH) of the investigated piperidols have lower frequencies than the corresponding values for the α isomers (equatorial OH) is also in agreement with the literature data (see [5, 6, 9]).

It follows from the data from the PMR spectra (see the experimental section) of both isomers of III that the 2-CH_3 group is equatorially oriented. The $J_{5a,6a}$ value of 11 Hz for the α isomer of III indicates an equatorial orientation of the 5-CH_3 group. We were unable to estimate the vicinal $J_{5,6}$ constant for the γ isomer of III because of superimposition of the signals of the 5-H proton and one of the protons in the 6 position. However, the known data [3, 10] (for nonsilylated 4-piperidols) make it possible to assume that the 5-CH_3 group in the γ isomers is equatorially oriented.

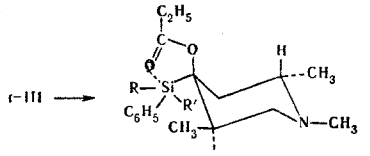


γ isomers α isomers

R = CH_3, R' = C_6H_5; II R = R' = CH_3; III R = R' = C_6H_5

Treatment of the γ isomers of piperidols I-III with propionyl chloride in benzene or propionic anhydride in xylene (and also in pyridine) gave their propionates (IV-VI, for pharmacological study).

Propionates IV-V practically are not hydrolyzed in either acidic or alkaline media, and this constitutes an exception as compared with all of the numerous esters of 4-piperidols.



I-III →

IV R = CH_3, R' = C_6H_5; V R = R' = CH_3; VI R = R' = C_6H_5

It is possible that this is explained by the formation of a stable chelate due to coordination of the carbonyl oxygen atom of the ester grouping and the silicon atom. It must also be noted that ester VI is a crystalline substance with a high melting point (228°), whereas all of the heretofore known propionates of tertiary and secondary 4-piperidols are liquids.

EXPERIMENTAL METHOD

Activity II aluminum oxide and an ethyl acetate–hexane system (1 : 3) were used for thin-layer chromatography (TLC). The IR spectra of KBr pellets and 10^{-1}–$3 \cdot 10^{-3}$ M solutions of the compounds in CCl_4 were recorded with a UR-20 spectrometer. The PMR spectra were obtained with an HA-100 spectrometer; carbon tetrachloride was used as the solvent for the γ isomer of III, and chloroform–deuteromethanol was used as the solvent for the α isomer of III. The internal standard was hexamethyldisiloxane.

1,2,5-Trimethyl-4-(methyldiphenylsilyl)-4-piperidol (I). A thoroughly filtered solution of methyldiphenylsilyllithium [from 7.63 g (1.1 g-atom) of lithium and 50 g (0.216 mole) of methyldiphenylchlorosilane in 300 ml of tetrahydrofuran (THF)] was added at 0° in the course of 45 min in a stream of nitrogen to a solution of 64.36 g (0.448 mole) of 1,2,5-trimethyl-4-piperidone in 100 ml of absolute THF, and the mixture was stirred at 20° for 1 h. It was then acidified (with respect to Congo red) with 18% hydrochloric acid, and the THF was removed by distillation. The neutral reaction products were extracted with ether. The residual salts of the organic bases were treated with a saturated solution of potassium hydroxide. The ether extract of the organic bases was worked up to give 25.9 g of the γ isomer of I with mp 136-137.5° (from hexane) and R_f 0.26. IR spectrum: 2795 ($N-CH_3$), 1430 and 1112 (SiC_6H_5), 790 and 1255 ($Si-CH_3$), 3335 (OH in crystals), 3591 (OH in solution), 965 (δ_{OH} in crystals), and 1012 and 1035 cm^{-1} (ν_{C-O} in crystals). Found: C 74.6; H 8.7; N 4.1; OH 5.4%. $C_{21}H_{29}NOSi$. Calculated: C 74.5; H 8.5; N 4.1; OH 5.0%. The picrate had mp 174.5-176° (from alcohol). Found: N 9.5%. $C_{21}H_{29}NOSi \cdot C_6H_3N_3O_7$. Calculated: 9.9%.

Distillation of the mother liquor remaining after separation of the isomer gave 32.3 g of the starting piperidone [bp 55-65° (5 mm) and n_D^{20} 1.4602]. The residue was crystallized from alcohol to give 1 g of the γ isomer of I (for an overall yield of 14%).

The mother liquor was treated with an alcohol solution of picric acid. Four crystallizations of the mixture of picrates of the isomers of I (alcohol with acetone) gave 1.3 g of the picrate of the α isomer of I with mp 213-214°. Found: N 9.9%. $C_{21}H_{29}NOSi \cdot C_6H_3N_3O_7$. The picrate was decomposed with a column filled with activity II aluminum oxide with elution by acetone to give 0.5 g (0.7%) of the α isomer of I with mp 109-110° (from heptane) and R_f 0.11. IR spectrum: 2810 and 2789 ($N-CH_3$), 1428 and 1109 ($Si-C_6H_5$), 1260 and 795 ($Si-CH_3$), 3135 (ν_{OH} in crystals), 3581 (ν_{OH} in solution), 988 (δ_{OH} in crystals), and 1021 and 1038 cm^{-1} (ν_{C-O} in crystals). Found: C 74.7; H 8.7; N 4.2%. $C_{21}H_{29}NOSi$. Calculated: C 74.5; H 8.5; N 4.1%.

1,2,5-Trimethyl-4-(dimethylphenylsilyl)-4-piperidols (II). Similarly, 5.75 g (0.83 g-atom) of lithium, 30.86 g (0.18 mole) of dimethylphenylchlorosilane, and 75 g (0.53 mole) of 1,2,5-trimethyl-4-piperidone in 270 ml of absolute THF gave 18.02 g (38%) of the γ isomer of II with mp 62.5-63° (from hexane) and R_f 0.28. IR spectrum: 3330 (ν_{OH} in crystals), 960 (δ_{OH} in crystals), and 1011 and 1035 cm^{-1} (ν_{C-O}). Found: C 69.3; H 10.0; N 5.3; Si 10.3; OH 5.9%. $C_{16}H_{27}NOSi$. Calculated: C 69.3; H 9.8; N 5.1; Si 10.1; OH 6.2%. The hydrochloride had mp 193-194° (from alcohol–acetone). Found: N 4.8; Cl 11.7%. $C_{16}H_{27}NOSi \cdot HCl$. Calculated: N 4.6; Cl 11.4%.

1,2,5-Trimethyl-4-(triphenylsilyl)-4-piperidol (III). This compound was obtained as described in [1]. The γ isomer had mp 99.5-100.1° and R_f 0.28. IR spectrum: 3400 (ν_{OH} in crystals), 3588 (ν_{OH} in solution), 960 (δ_{OH} in crystals), and 1008 and 1031 cm^{-1} (ν_{C-O} in crystals). PMR spectrum: δH_{3a} 1.31-161 (quartet) and H_{3e} 1.70-1.86 ppm; $J_{3,3} = 13.5$, $J_{3a,2a} = 10$, and $J_{3e,2a} = 3.0$ Hz. The α isomer had mp 156-157° and R_f 0.08. IR spectrum: 3130 (ν_{OH} in crystals), 3575 (ν_{OH} in solution), 982 (δ_{OH} in crystals), and 1015 and 1043 cm^{-1} (ν_{C-O} in crystals). PMR spectrum: δH_{3a} 1.32-1.56 (quartet) and H_{6a} 1.63-1.85 ppm (triplet); $J_{3,3} = 13.5$, $J_{3a,2a} = 10$, $J_{6,6} = 11$, and $J_{5a,6a} = 11$ Hz.

1,2,5-Trimethyl-4-(methyldiphenylsilyl)-4-propionyloxypiperidine (IV). A 4.3-g (12.7 mmole) sample of the γ isomer of I and 6.5 g (50 mmole) or propionic anhydride were heated in 12 ml of pyridine at 140-150° for 16 h, after which the pyridine and propionic anhydride were removed by distillation, and the residue was treated with saturated sodium carbonate solution. The organic bases were extracted with ether and converted to the hydrochlorides. Three recrystallizations from ethyl acetate gave 1.7 g (32%) of the hydrochloride of IV with mp 195-197° (dec.) and R_f 0.65. IR spectrum: 1730 (C=O), 1431 and 1110 $Si-C_6H_5$), and 1258 and 803 cm^{-1} ($Si-CH_3$). Found: N 3.5; Cl 8.1%. $C_{24}H_{33}NO_2Si \cdot HCl$. Calculated: N 3.2; Cl 8.2%.

1,2,5-Trimethyl-4-(dimethylphenylsilyl)-4-propionyloxypiperidine (V). A 5-g (18 mmole) sample of the γ isomer of II and 4.33 g (33 mmole) of propionic anhydride were heated in 25 ml of absolute xylene at 140° for 16 h. The mixture was then worked up as in the preparation of IV to give 2.62 g (39%) of the hydrochloride of V with mp 190-191° (from ethyl acetate) and R_f 0.75. IR spectrum: 1725 (C=O), 1428 and 1110 ($Si-C_6H_5$), 1260, 1246, and 810 cm^{-1} [$Si(CH_3)_2$]. Found: C 61.3; H 8.5; N 3.6; Cl 9.9%. $C_{19}H_{31}NO_2Si \cdot HCl$. Calculated: C 61.7; H 8.7; N 3.8; Cl 9.6%. The yield of the hydrochloride in the case of acylation with propionyl chloride was 15%.

1,2,5-Trimethyl-4-(triphenylsilyl)-4-propionyloxypiperidine (VI). A 0.99-g (2.5 mmole) sample of the γ isomer of III and 1.1 g (7.8 mmole) of propionic anhydride were heated in 2 ml of pyridine at 140-150°

for 10 h, after which the pyridine and excess propionic anhydride were removed by distillation. The residue was crystallized from ligroin–benzene (1 : 1) to give 0.5 g (44%) of VI with mp 228° and R_f 0.54. IR spectrum: 1725 (C=O) and 1428 and 1105 cm^{-1} (Si–C_6H_5). Found: C 76.1; H 8.1; N 3.4%. $C_{29}H_{35}NO_2Si$. Calculated: C 76.1; H 7.7; N 3.1%. The picrate had mp 224.5-226° (from alcohol–acetone). Found: N 8.0%. $C_{29}H_{35}NO_2Si \cdot C_6H_3N_3O_7$. Calculated: N 8.2%. The hydrochloride had mp 242-243° (from alcohol–acetone). Found: C 70.7; H 7.1; N 3.1; Cl 7.4%. $C_{29}H_{35}NO_2Si \cdot HCl$. Calculated: C 70.5; H 7.3; N 2.8; Cl 7.2%.

LITERATURE CITED

1. N. S. Prostakov and A. V. Varlamov, Khim. Geterotsikl. Soedin., No. 12, 1637 (1970).
2. M. M. A. Hassan and A. F. Casy, Org. Magn. Res., 2, 197 (1970).
3. N. S. Prostakov and N. N. Mikheeva, Usp. Khim., 31, 1191 (1962).
4. I. N. Nazarov, N. S. Prostakov, and N. I. Shvetson, Zh. Obshch. Khim., 26, 2798 (1956).
5. E. Eliel, N. Allinger, S. Angyal, and T. Morrison, Conformational Analysis, Wiley (1965).
6. J. Hajdukovic, J. Regnier, and M. L. C. Martin, Compt. Rend., C, 272, 330 (1971).
7. G. R. Clemo and K. H. Jack, Chem. Ind., 195 (1953).
8. B. L. Lenitz, C. M. Martini, M. Prizner, and P. C. Nachod, J. Amer. Chem. Soc., 74, 5564 (1952).
9. R. Granger, J. P. Chapat, F. Simon, J. P. Lizad, and P. Loycux, Compt. Rend., C, 272, 337 (1971).
10. N. S. Prostakov, B. E. Zaitsev, N. M. Mikhailov, and N. N. Mikheeva, Zh. Obshch. Khim., 34, 463 (1964).

SYNTHESIS OF INDOLIZINES AND PYRIDINIUM YLIDS FROM 4,5-DISUBSTITUTED α-PICOLINES

N. S. Prostakov, L. A. Gaivoronskaya, Kamara Maiga Sarata Mokhomon, V. P. Zvolinskii, A. A. Savina, Munzer Makhsida, and Victor Hugo Opaso Karrasko

UDC 547.82'83'759.07

New 1,3-diacetylindolizines were obtained from 4-phenyl- and 4-benzyl-2,5-dimethylpyridines; some transformations involving their acetyl groups were realized. The same pyridine bases were used in syntheses of pyridinium ylids. The transformations of the latter to indolizines were studied.

Of the rather large number of synthesized indolizines, there are few that have substituents in the six-membered ring. This is explained, first, by the low degree of accessibility of substituted α-picolines and, second, by the occurrence of electrophilic substitution reactions in the five-membered ring of indolizines. Using our previously obtained 4-phenyl- and 4-benzyl-2,5-dimethylpyridines (I, II) [1, 2] we synthesized new pyridinium ylids and indolizines with substituents in the pyridine ring.

7-Phenyl- and 7-benzyl-6-methyl-1,3-diacetylindolizines (III, IV) were obtained by the Scholtz method [3] from pyridines I and II. Only the carbonyl group attached to C_1 undergoes reaction in the reaction of III and IV with phenylhydrazine, and hydrazones V and VI, respectively, are isolated. When alkali is present, both acetyl groups of indolizine III undergo condensation with benzaldehyde to give 6-methyl-7-phenyl-1,3-dicinnamoylindolizine (VII). However only 6-methyl-7-phenyl-3-acetyl-1-(p-dimethylaminocinnamoyl)indolizine (VIII) was isolated in low yield in the condensation with p-dimethylaminobenzaldehyde under similar conditions. The structure of indolizines III-VIII was confirmed by the spectral data (see the experimental section).

Patrice Lumumba International-Friendship University, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 506-510, April, 1976. Original article submitted January 3, 1975; revision submitted June 5, 1975.