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STEREOSELECTIVE SYNTHESIS OF 2*e*-PHENYL-4*e*-HYDROXY-1-AZASPIRO[5.5]UNDECANE

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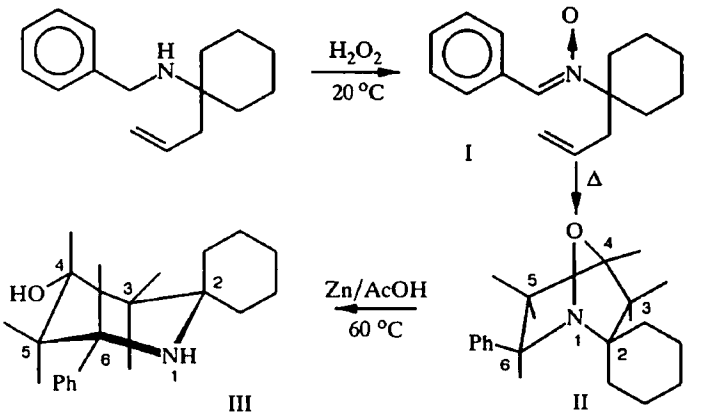
6-Phenylspiro(1-aza-7-oxabicyclo[2.2.1]heptane-2-cyclohexane) was synthesized by cyclization of N-benzylidene-1-allyl-1-cyclohexylamine N-oxide, and its reduction splitting yielded 2e-phenyl-4e-hydroxy-1-azaspiro[5.5]undecane.

Intramolecular cycloaddition of alkenes to nitrons is an efficient method of constructing hinged bridge systems [1-4]. Due to the high regio- and stereospecificity of formation of adducts and ease of transformation of their isoxazolidine fragment, this reaction was used in synthesis of complex structures, for example, the alkaloid luciduline [5], prostaglandins [6], secoishvaranol-12 sesquiterpene [3], and ambrosin [7].

Synthesis of 2-phenyl-1-aza-7-oxabicyclo[2.2.1]heptane by thermal cyclization of N-benzylidene-3-butenamine N-oxide was described for the first time in [1]. Bicycloheptane was transformed into *cis*-1-methyl-2-phenylpiperidin-4-ol by successive hydrogenolysis and N-methylation. It was later found [2] that thermal cyclization of N-benzylidene(undecylidene)(3-trimethylsilyl-4-pepten-2-yl)amines results in the formation of a mixture of isomeric (with respect to the position of the substituents) 1-aza-7-oxabicyclo[2.2.1]heptanes, whose hydrogenolysis yielded a mixture of isomeric (with respect to the position of the substituents) piperidin-4-ols.

We used the strategy of the researchers in [1] to construct 2*e*-phenyl-4*e*-hydroxy-1-azaspiro[5.5]undecane — the spiro(piperidine-2-cyclohexane) system on which the alkaloids histrionicotoxin and perhydrohistrionicotoxin are based [8, 9].

Nitron I was obtained by oxidation of 1-benzylamino-1-allylcyclohexane [10] with hydrogen peroxide in the presence of sodium tungstate [11] with a yield of 53%.



Compound 1 was quantitatively transformed into 6-phenylspiro(1-aza-7-oxabicyclo[2.2.1]heptane-2-cyclohexane) (II) on boiling in heptane, and its reduction splitting yields 2*e*-phenyl-4*e*-hydroxy-1-azaspiro[5.5]undecane (III) with a yield of 76%.

The IR spectrum of nitron I exhibits an intense band of N→O stretching vibrations at 1140 cm^{-1}, not present in the spectrum of bicyclic compound II. The IR spectrum of the latter is characterized by the presence of an intense band of N−O

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at 1296 cm^{-1}. There are two broad bands of stretching vibrations of a bound OH group with maxima at 3284 and 3174 cm^{-1} in the IR spectrum of piperidol III. The NH group in compound III is sterically shielded by bulky substituents, which causes the appearance of a narrow band of vibrations of a free N–H bond at 3480 cm^{-1} in the IR spectrum.

The mass spectrum* of nitron I exhibits the peak of molecular ion 243 (18*) and peaks of fragmentary ions 120 (11) and 123 (9) caused by splitting of the M^+ ion at the N–C bond. These ions subsequently eliminate OH and H, yielding fragments 103 (49) and 122 (21). The other direction of splitting of the M^+ion of compound I is related to splitting of the allyl substituent with localization of the charge on it.

The mass spectrum of bicyclic compound II is characterized by the presence of the peak of molecular ion 243 (10) and intense fragmentary ions $C_6H_5-CH=CH_2^+$, $CH_2=C(CH_2)_5^+$, and $C_6H_5CH_2^+$ [104 (49), 96 (19), and 91 (88)], caused by α- and β-cleavage of the bicyclic fragment. In addition, there are intense peaks 77 (70) and 78 (30) corresponding to phenyl and benzene in the mass spectrum.

There is molecular ion peak 245 (16) corresponding to its empirical formula in the mass spectrum of spiro(piperidolcyclohexane) III. The basic directions of its fragmentation are related to elimination of $H^{\cdot}$, $HO^{\cdot}$, and $C_6H_5^+$. The intensity of the last peak is 49%. The ions $[M-H]^+$ and $[M-OH]^+$ subsequently split $C_6H_5C\equiv NH^+$ [104 (43)] and C_6H_5CN [103 (24)]. In addition, peaks of the ions $[M-29]^+$, $[M-43]^+$, and $[M-57]^+$ of different intensity, caused by fragmentation of the cyclohexane ring, are observed in the mass spectra of compounds I-III.

The presence of four proton multiplets [HC=C (5.66), H_{trans} (5.08), H_{cis} (5.06), and CH_2(2.59 ppm)] with characteristic SSCC ($J_{CH,CH}$, $J_{CH,Htrans}$, $J_{CH,Hcis}$) in the PMR spectrum indicates preservation of the allyl fragment during oxidation.

The signals in the spectrum of compound II were assigned by comparing the chemical shifts and vicinal SSCC with the data for 2-methyl-3-trimethylsilyl-6-R-1-aza-7-oxabicyclo[2.2.1]heptanes [2], which have a similar bicyclic skeleton of the molecule. Substitution of the solvent $CDCl_3$ by C_6D_6 is because the values of the chemical shifts of the 5_{endo}-H and 5_{exo}-H protons in a solution of $CDCl_3$ are relatively close (~2.04 ppm) and the signals of the protons having spin coupling with them belong to spectra of a higher order. The SSCC measured in the approximation of first-order spectra differ significantly from the real spectra (see Experimental section below), which makes a comparison of these values with the published data invalid. In a solution of C_6D_6, the 5_{endo}-H and 5_{exo}-H chemical shifts differ by 44 Hz, which allows analyzing the spectrum with respect to the first order and comparing the measured SSCC with the published data. The values of the vicinal SSCC of $J_{5,6}$, equal to 8.2 and 4.3 Hz, are close to the corresponding values of $J_{5\text{-endo, }6\text{-endo}}$ (8.2-8.3) and $J_{5\text{-exo, }6\text{-endo}}$ (5.2-5.6 Hz) described in [2], which indicates the *exo*-position of the phenyl substituent in compound II. In the case of the *endo*-position of the phenyl radical, the values of $J_{5,6}$ would be close to the SSCC of $J_{5\text{-endo, }6\text{-exo}}$ of 6.6 and $J_{5\text{-exo, }6\text{-exo}}$ of 10.1 Hz [2].

There are two multiplets assigned to 4-H and 6-H protons, respectively, in the PMR spectrum of piperidol III at 4.00 and 3.87 ppm. The more weak-field signal has a triplet–triplet structure due to axial–axial ($J_{3a,4a} = J_{4a,5a} = 11.6$ Hz) and axial–equatorial ($J_{3e,4a} = J_{4a,5e} = 4.6$ Hz) interaction constants. The presence of axial–axial constants for the 4-H proton indicates the equatorial position of the hydroxyl group. The doublet–doublet signal of the 6-H proton is also characterized by the presence of an axial–axial interaction ($J_{5a,6a} = 11.6$ Hz), which indicates the equatorial position of the phenyl substituent at $C_{(6)}$. The higher values of the axial–axial SSCC (11.6 Hz) indicate that piperidol III exists in the solution primarily in the chair conformation. The paired equality of the vicinal SSCC $J_{3e,4a} = J_{4a,5e} = 4.6$ and $J_{3a,4a} = J_{4a,5a} = J_{5a,6a} = 11.6$ Hz could indicate that the piperidone skeleton of molecule III is symmetric relative to the vertical plane passing through atoms $N_{(1)}$ and $C_{(4)}$.

We note that the assignment of the signals in the PMR spectra to concrete protons in molecules II and III was confirmed by the double resonance spectra.

Preparative synthesis of the spiro(piperidine-2-cyclohexane) system substituted at the piperidine fragment was thus conducted.

EXPERIMENTAL

The IR spectra were made on a UR-20 in KBr pellets. The PMR spectra were recorded for 2% solutions on a Bruker WP-200 spectrometer at 20°C (in $CDCl_3$ or C_6D_6, TMS internal standard). The mass spectra were made on a Varian MAT-112

*Here and below, the *m/z* (relative intensity, %) are given for the ion peaks.

(direct introduction, at 70 eV). Silufol UV-254 plates were used for TLC, and Al_2O_3, 0 deg. activity, was used for column chromatography.

N-Benzylidene(1-allylcyclohexyl-1)amine N-Oxide (I). Here 0.74 g (2.2 mmole) of $Na_2WO_4 \cdot 2H_2O$ and 18 ml (176 mmole) of 30% hydrogen peroxide with cooling with water were added to a solution of 10 g (44 mmole) of *gem*-benzylaminoallylcyclohexane in 30 ml of acetone. It was stirred at 20°C for 4 days (TLC monitoring). Then 20 ml of water was added and the nitron was extracted with ether (3 × 50 ml) and dried with $MgSO_4$. After distillation of the ether, the residue was purified on a plate with Al_2O_3 (4 × 4 cm), heptane eluent, yielding 5.74 g (53%) of compound I, a yellow oil, R_f = 0.28 (ethyl acetate–hexane, 1:10). On standing the oil crystallized, yielding colorless crystals with mp = 36-38°C.

IR spectrum: 954 (N–O), 1140 (N–O), 1577 (C=N), 1649 cm^{-1} (C=C). PMR spectrum ($CDCl_3$): 8.30 (2H, m, *o*-H_{Ph}); 7.45 (3H, m, *m,p*-H_{Ph}); 7.39 (1H, s, HC=N); 5.66 (1H, m, $J_{CH2,CH}$ = 7.6, $J_{CH,Htrans}$ = 17.0, $J_{CH,Hcis}$ = 10.0 Hz, HC=C); 5.08 (1H, d, $J_{CH,Htrans}$ = 17.0 Hz, H_{trans}); 5.06 (1H, d, $J_{CH,Hcis}$ = 10.0 Hz, H_{cis}); 2.59 (2H, d, $J_{CH2,CH}$ = 7.6 Hz, CH_2); 1.85 ppm (10 H, m, C_6H_{10}). Mass spectrum, *m/z* (I_{rel}, %): 243 (M^+, 18), 214 (10), 200 (21), 186 (16), 131 (49), 129 (32), 123 (9), 122 (21), 120 (11), 104 (57), 103 (49), 82 (21), 81 (47), 79 (38), 78 (49), 77 (80). Found, %: C 78.85; H 8.50; N 5.70. $C_{16}H_{21}NO$. Calculated, %: C 79.00; H 8.64; N 5.76.

6-Phenylspiro(1-aza-7-oxabicyclo[2.2.1]heptane-2-cyclohexane) (II). A solution of 3.2 g (13.2 mmole) of nitron I in 20 ml of heptane was boiled for 6 h. It was cooled, and 2.34 g of spiro compound II was filtered off. The filtrate was boiled for 4 h longer, and an additional 0.33 g of compound II was separated after cooling, yielding 2.67 g (83%) of spiro compound II, colorless crystals, mp = 88.5-89°C (from heptane), R_f = 0.53 (ethyl acetate–hexane, 1:10). IR spectrum: 1296 cm^{-1} (N–O). PMR spectrum (C_6D_6): 7.44 (2H, m, *o*-H_{Ph}); 6.9-7.2 (3H, m, *m, p*-H_{Ph}); 4.31 (1H, t, $J_{3\text{-exo},4} = J_{4,5\text{-exo}}$ = 5.2 Hz, 4-H); 4.14 (1H, d.d, $J_{5\text{-endo, 6-endo}}$ = 8.2, $J_{5\text{-exo, 6-endo}}$ = 4.3 Hz, 6_{endo}-H); 1.63 (1H, d.d.d.d, $J_{5\text{-endo},5\text{-exo}}$ = 11.3; $J_{4,5\text{-exo}}$ = 5.2; $J_{5\text{-exo},6\text{-endo}}$ = 4.3; $J_{3\text{-exo},5\text{-exo}}$ = 2.4 Hz; 5_{exo}-H); 1.41 (1H, d.d, $J_{5\text{-endo, 5-exo}}$ = 11.3; $J_{5\text{-endo},6\text{-endo}}$ = 8.2 Hz, 5_{endo}-H); 1.34 (1H, d.d.d, $J_{3\text{-endo},3\text{-exo}}$ = 11.3; $J_{3\text{-exo},4}$ = 5.2; $J_{3\text{-exo},5\text{-exo}}$ = 2.4 Hz, 3_{exo}-H); 0.58 (1H, d, $J_{3\text{-endo},3\text{-exo}}$ = 11.3 Hz, 3_{endo}-H); 1.45 ppm (10H, m, C_6H_{10}). PMR spectrum (*: measured in the approximation of first-order spectra; $CDCl_3$): 7.3 (5H, m, H_{Ph}); 4.89 (1H, d.t, $J_{3\text{-exo},4}$ = 5.3, $J^*_{4,5\text{-endo}} \sim J^*_{4,5\text{-exo}} \sim$ 2.6 Hz, 4-H); 4.50 (1H, t, $J^*_{5\text{-endo},6\text{-endo}} \sim J^*_{5\text{-exo},6\text{-endo}} \sim$ 6.3 Hz, 6_{endo}-H); ~2.04 (2H, m, $J^*_{4,5\text{-endo}} \sim J^*_{4,5\text{-exo}} \sim$ 2.6, $J^*_{5\text{-endo},6\text{-endo}} \sim J^*_{5\text{-exo},6\text{-endo}} \sim$ 6.3 Hz, 5_{endo}-H, 5_{exo}-H); 1.82 (1H, d.d, $J_{3\text{-endo},3\text{-exo}}$ = 11.3, $J_{3\text{-exo},4}$ = 5.3 Hz, 3_{exo}-H); 1.23 (1H, d, $J_{3\text{-endo},3\text{-exo}}$ = 11.3 Hz, 3_{endo}-H); 1.55 ppm (10H, m, C_6H_{10}). Mass spectrum, *m/z* (I_{rel}, %): 243 (M^+, 10) 214 (2), 200 (9), 186 (7), 122 (39), 118 (19), 117 (22), 106 (33), 104 (49), 96 (19), 91 (88), 83 (20), 82 (24), 81 (71), 79 (33), 78 (30), 77 (70), 41 (100). Found, %: C 78.91; H 8.74; N 6.00. $C_{16}H_{21}NO$. Calculated, %: C 79.00; H 8.64; N 5.76.

2*e*-Phenyl-4*e*-hydroxy-1-azaspiro[5.5]undecane (III). A mixture of 1 g (4.1 mmole) of compound II, 2.7 g (41.15 mmole) of zinc, and 47 ml (0.82 mole) of acetic acid was heated for 6 h (TLC monitoring) at 65-70°C. Then 20 ml of a saturated solution of soda was added to the residue after distillation of the acid and it was extracted with ether (4 × 50 ml) and dried with $MgSO_4$. After distillation of the ether, the residue was crystallized from heptane, yielding 0.77 g (76%) of compound III, colorless crystals, mp = 102.5-103.5°C, R_f = 0.51 (ethyl acetate). IR spectrum: 3280 (OH), 3174 (OH), 3480 cm^{-1} (NH). PMR spectrum ($CDCl_3$): 7.35 (5H, m, H_{Ph}); 4.00 (1H, t.t, $J_{3a,4a} = J_{4a,5a}$ = 11.6; $J_{3e,4a} = J_{4a,5e}$ = 4.6 Hz, 4*a*-H); 3.87 (1H, d.d, $J_{5a,6a}$ = 11.6; $J_{5e,6a}$ = 2.4 Hz, 6*a*-H); 2.14 (1H, d.d.t, $J_{5a,5e}$ = 11.6, $J_{4a,5e}$ = 4.6, $J_{5e,6a} = J_{3e,5e}$ = 2.4 Hz, 5*e*-H); 2.04 (1H, d.d.d, $J_{3a,3e}$ = 11.6, $J_{3e,4a}$ = 4.6, $J_{3e,5e}$ = 2.4 Hz, 3*e*-H); 1.39 (1H, q, $J_{5a,5e} = J_{4a,5a} = J_{5a,6a}$ = 11.6 Hz, 5*a*-H); 1.14 (1H, t, $J_{3a,3e} = J_{3a,4a}$ = 11.6 Hz, 3*a*-H); 1.5 ppm (10H, m, C_6H_{10}). Mass spectrum, *m/z* (I_{rel}, %): 245 (M^+, 16), 244 (1.4), 228 (6), 216 (3), 202 (100), 189 (40), 188 (9), 144 (13), 133 (16), 115 (16), 106 (25), 104 (43), 103 (24), 91 (37), 79 (30), 78 (19), 77 (49). Found, %: C 78.00; H 9.16; N 5.35. $C_{16}H_{23}NO$. Calculated, %: C 78.36; H 9.39; N 5.71.

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