SYNTHESIS OF NITROXYL RADICALS BASED ON 4-ETHYNYL-4-HYDROXY-2,2,6,6-TETRAMETHYLPIPERIDINE

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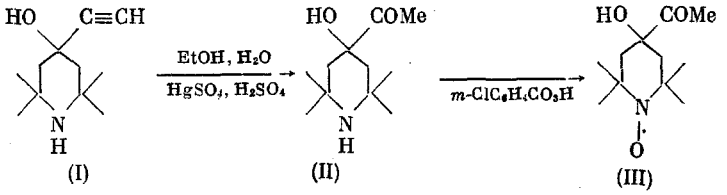
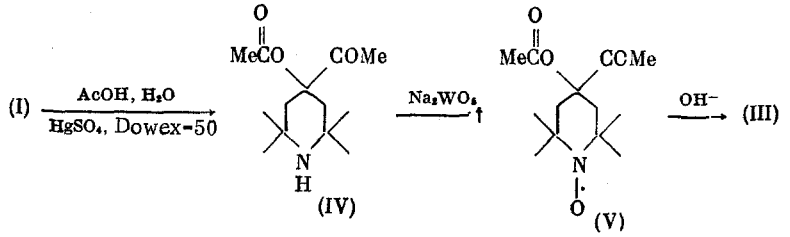
The accessibility of 4-ethynyl-4-hydroxy-2,2,6,6-tetramethylpiperidine (I) [1] and the variety of the products from the transformation of acetylenic carbinols [2] open the possibility for the synthesis of various functional derivatives of nitroxyl radicals (NR) from (I). The products may find use as spin labels [3], paramagnetic complexing agents [4, 5], and diene [6], vinylacetylene, and α-oxide spin-labelled monomers.

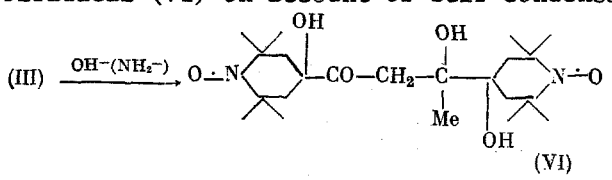
In the present work we investigated the products from the hydrogenation, hydration, and dehydration of compound (I). During Kucherov hydration of compound (I) 2,2,6,6-tetramethyl-4-hydroxy-4-acetylpiperidine (II) is obtained. Instead of the expected 2,2,6,6-tetramethyl-4-hydroxy-4-acetyl-1-piperidinoxyl (III) the oxidation of compound (II) by pertungstic acid gives the products from oxidative cleavage with m/e 170 and 83. The transformation of (II) to (III) occurs under the influence of m-chloroperbenzoic acid but with a small yield (37.3%):



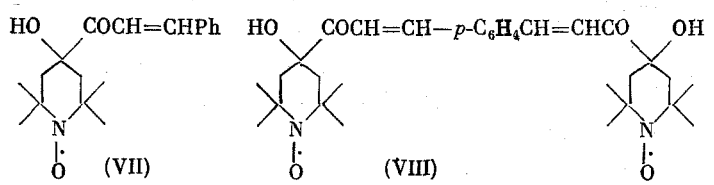
The synthesis of (III) is easily realized by the following scheme:



In the presence of catalytic amounts of alkali or sodium amide the ketol radical (III) is converted into the aldol biradical (VI) on account of self-condensation:



It is interesting that dimethylacetylcarbinol enters into the crotonic self-condensation under these conditions [7]. The hyperfine structure in the ESR spectrum of compound (VI) (Fig. 1) includes seven lines, which indicates intramolecular spin—spin coupling of the N–O groups, $J \geqslant a$. Like dimethylacetylcarbinol, compound (III) reacts with benzaldehyde and terephthalaldehyde, forming the products from crotonic condensation:



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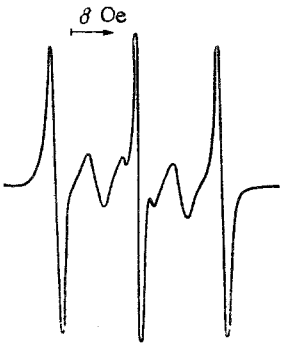
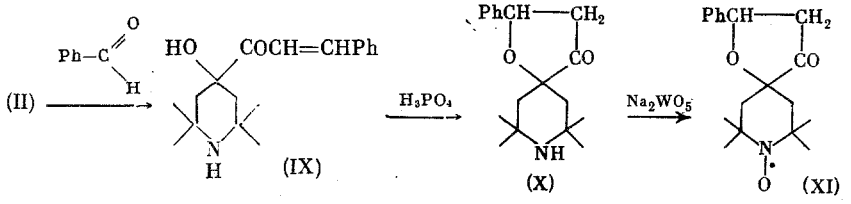
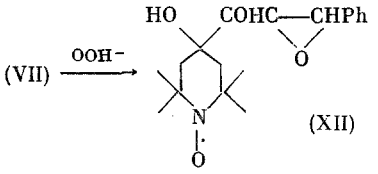


Fig. 1. The ESR spectrum of the aldol biradical (VI).

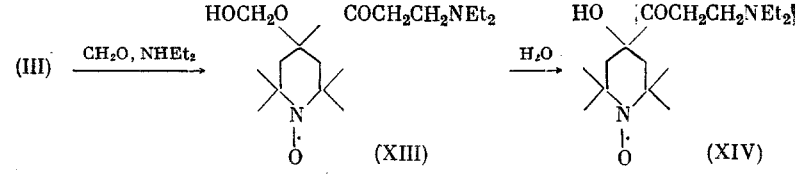
The analogous reaction of compound (II) with benzaldehyde gave the benzylidene derivative (IX). The latter was converted by the action of phosphoric acid into the piperidylfuranone (X) and then by oxidation with Na_2WO_5 into the nitroxyl (XI):



Under the conditions of the Weitz and Scheffer reaction [8] compound (VII) is epoxidized to the paramagnetic keto oxide (XII):

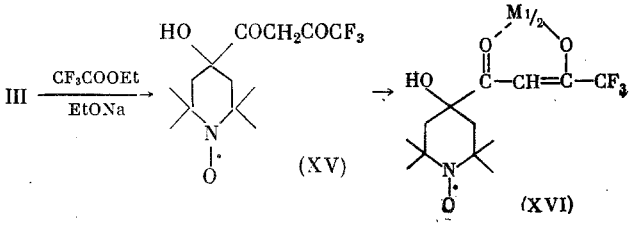


The paramagnetic ketol (III) behaves uniquely in the Mannich reaction. In addition to aminomethylation of the COMe group hydroxymethylation of the OH group occurs with the formation of (XIII). When boiled in water at pH 4, this compound is rapidly converted into the Mannich base (XIV):



Compounds (XIII) and (XIV) readily form methiodides, which can be used as alkylating spin labels [9].

With trifluoroethyl acetate compound (III) forms the paramagnetic trifluoro-β-diketone (XV), isolated in the form of the copper and cobalt complexes (XVI):



Dehydration does not occur when the ketol (III) is heated in DMFA in the presence of potassium acetate and the imino ketol (II) is heated in 50-70% sulfuric acid. Compounds (XVIII) and (XIX) corresponding to their dehydration products were obtained according to the following scheme:

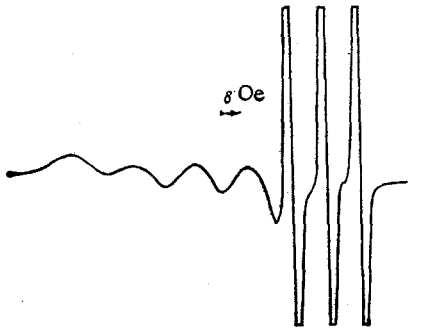


Fig. 2

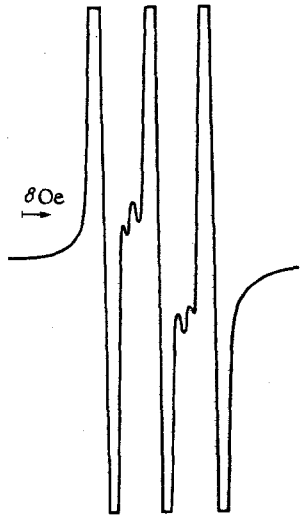
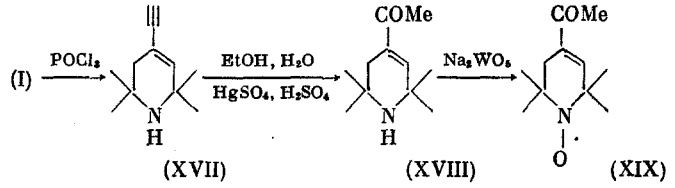


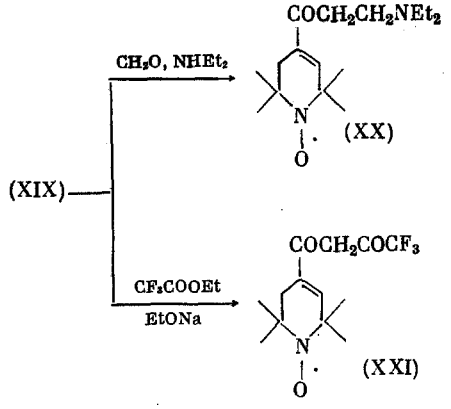
Fig. 3

Fig. 2. The ESR spectrum of the complex of the paramagnetic trifluoro-β-diketone (XXI) with the Cu^{2+} ion.

Fig. 3. The ESR spectrum of the complex of the paramagnetic trifluoro-β-diketone (XXI) with the Co^{2+} ion.



The ketone (XIX) readily enters into the Mannich and Claisen reactions:



Compound (XXI) forms stable paramagnetic complexes (XXII) with Cu^{2+} and Co^{2+} ions:

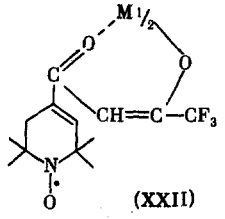
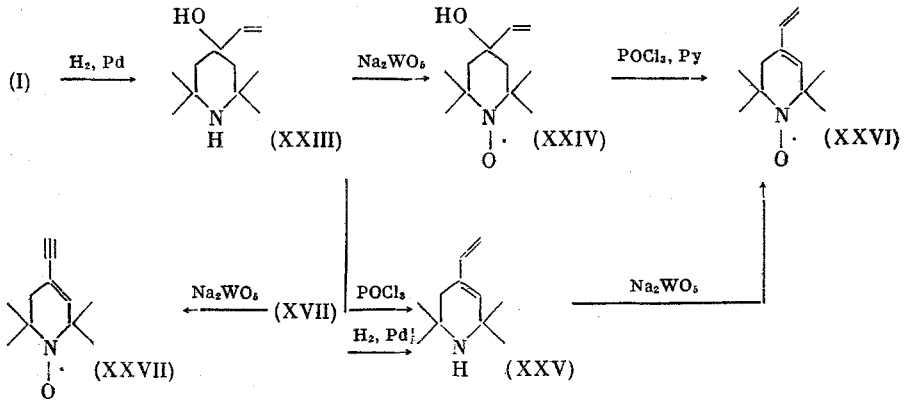


Figure 2 shows the ESR spectra of the complexes of (XXI) with Cu^{2+} and Co^{2+} ions. The poorly resolved hfs of the Cu complex with $\Delta H = 27$ Oe is due to isotropic interaction between the unpaired electron and the copper nucleus ($J = 3/2$). The triplet with splitting of 15.6 Oe and $g = 2.006$ is due to iminoxyl radicals not taking part in exchange. The fraction of such uncombined radical groups amounts to 2-3%. The hyperfine structure of the ESR spectrum of

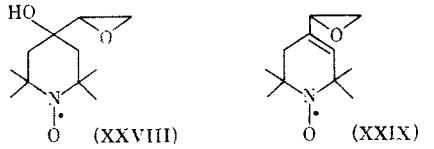
the Co complex (Fig. 3) includes seven lines, and this is explained by intramolecular spin–spin exchange between the two paramagnetic fragments of the ligands.

Thus, in contrast to the 2,2,6,6-tetramethyl-4-oxo-1-piperidinoxyl, the paramagnetic ketones obtained from (I) are more reactive and make it possible to obtain interesting nitroxyl radicals for molecular biology and analytical chemistry.

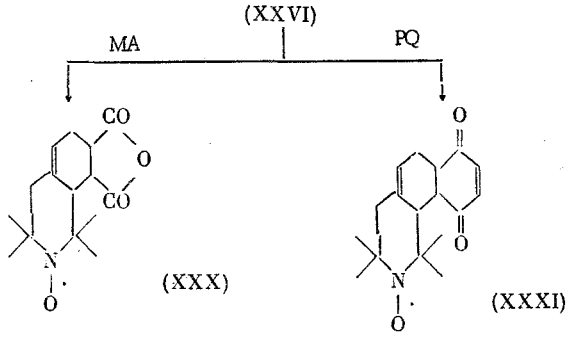
Of no lesser interest are the products from selective hydrogenation and dehydration of compound (I):



The nitroxyls (XXIV) and (XXVI) are epoxidized by m-chloroperbenzoic acid to the α-oxides (XXVIII) and (XXIX):



The diene nitroxyl (XXVI) enters into the diene synthesis reaction with maleic anhydride (MA) and p-quinone (PQ), forming the paramagnetic adducts (XXX) and (XXXI):



EXPERIMENTAL

The initial 2,2,6,6-tetramethyl-4-hydroxy-4-ethynylpiperidine was synthesized by the method in [1]. The IR spectra were recorded on a UR-20 instrument. The mass spectra were recorded on an RMU-6D instrument. The ESR spectra were recorded on an EPRB-IKhF instrument.

2,2,6,6-Tetramethyl-4-hydroxy-4-acetylpiperidine (II). To a boiling mixture of 20 ml of ethanol, 6 ml of concentrated sulfuric acid, 6 ml of water, and 3 g of mercuric sulfate we added dropwise a solution of 10 g of compound (I) in 100 ml of ethanol. The mixture was boiled for 4 h and filtered. The filtrate was made alkaline to pH 9 and extracted with benzene. The extract was dried with potassium carbonate and evaporated under vacuum. The residue gave 5.7 g (51.8%) of compound (II); mp 131-132°C (from hexane). Found %: C 66.51; H 10.41; N 6.96. mol.wt. 199 [by mass spectrometry (MS)]. $C_{11}H_{21}NO_2$. Calculated %: C 66.33; H 10.55; N 7.03. IR spectrum (ν, cm^{-1}): 1700 (C=O).

2,2,6,6-Tetramethyl-4-hydroxy-4-acetyl-1-piperidinoxyl (III). a. A 4-g sample of compound (V) was dissolved in 100 ml of a boiling 10% aqueous solution of sodium hydroxide.

After cooling, the mixture was extracted with ether, the extract was dried with sodium sulfate, and the solvent was evaporated under vacuum. The residue gave 2.5 g (74.8%) of (III); mp 75°C (from hexane). Found %: C 61.54; H 9.41; N 6.50. mol.wt. 214 (MS). $C_{11}H_{20}NO_3$. Calculated %: C 61.68; H 9.35; N 6.54. IR spectrum (ν, cm^{-1}): 1700 (C=O), 1310 (C—O of tertiary alcohol), 3130 (OH).

b. To a solution of 0.5 g of (II) in 50 ml of dry chloroform, cooled to 0°C, we added 1 g of 82% m-chloroperbenzoic acid. The mixture was left at 0°C overnight, washed with a 40% solution of sodium bicarbonate and twice with water, and dried with sodium sulfate. The solvent was evaporated under vacuum. The syrupy red residue was dissolved in benzene and chromatographed on silica gel LS100/160. The product was eluted with a 9:1 mixture of chloroform and methanol. The fraction with R_f 0.60 was collected. A 0.2-g yield of (III) was obtained in the form of orange crystals; mp 75°C (from hexane). Found %: C 61.49; H 9.50; N 6.53. $C_{11}H_{20}NO_3$. Calculated %: C 61.68; H 9.35; N 6.54.

2,2,6,6-Tetramethyl-4-acetoxy-4-acetylpiperidine (IV). A mixture of 5 g of compound (I), 1 ml of water, 2 g of Dowex-50 (H^+ form) impregnated with 1 g of mercuric sulfate, and 25 ml of glacial acetic acid was boiled for 2 h and filtered. The filtrate was made alkaline to pH 9 and extracted with ether. The extract was dried with sodium sulfate, the ether was evaporated under vacuum, and the residue was recrystallized from hexane. A 4.85-g yield (72.9%) of (IV) was obtained; mp 81.5-82.5°C. Found %: C 64.61; H 9.86; N 5.55. mol.wt. 241 (MS). $C_{13}H_{23}NO_3$. Calculated %: C 64.70; H 9.56; N 5.80. IR spectrum (ν, cm^{-1}): 1205, 1222, 1250 (C—O acetate), 1715 (C=O keto group), 1732 (C=O ester).

2,2,6,6-Tetramethyl-4-acetoxy-4-acetyl-1-piperidinoxyl (V). An 8-g sample of (IV) was dissolved in 150 ml of water, and 7 g of Na_2WO_4 and 12 ml of 30% hydrogen peroxide were added. After 24 h the pink crystals which separated were removed and recrystallized from hexane. An 8-g yield (94.2%) of (V) was obtained; mp 108-108.5°C. Found %: C 61.31; H 8.70; N 5.38. mol. wt. 256 (MS). $C_{13}H_{22}NO_4$. Calculated %: C 60.90; H 8.65; N 5.46.

1,3-Bis(2',2',6',6'-tetramethyl-1'-oxyl-4'-hydroxy-4'-piperidyl)-3-hydroxy-3-methyl-1-propanone (VI). A 1-g sample of compound (III) was dissolved in 20 ml of methanol, a little potassium hydroxide was added, and the mixture was boiled for 10 h. The alcohol was distilled, and the residue was dissolved in benzene and chromatographed on silica gel LS 100/160. The fraction with R_f 0.34 was collected (with a 9:1 mixture of chloroform and methanol as eluent). A 0.6-g yield (60%) of (VI) was obtained; mp 103-105°C. Found %: C 61.56; H 9.67; N 6.42. mol.wt. 428 (MS). $C_{22}H_{40}N_2O_6$. Calculated %: C 61.68; H 9.35; N 6.54.

2,2,6,6-Tetramethyl-4-hydroxy-4-benzylideneacetyl-1-piperidinoxyl (VII). A mixture of 1.07 g of (III), 0.53 g of freshly distilled benzaldehyde, 0.069 g of sodium, and 25 ml of absolute methanol was boiled for 10 h. The product was treated with water, the alcohol was evaporated under vacuum, the residue was extracted with ether, and the extract was dried with sodium sulfate. After distillation of the ether 0.8 g (56.7%) of (VII) was obtained; mp 110.5-111.5°C (from hexane). Found %: N 4.38. mol.wt. 302 (MS). $C_{18}H_{24}NO_3$. Calculated %: N 4.63. IR spectrum (ν, cm^{-1}): 1620 (C=C), 1680 (C=O conj.), 1455, 1495, 1580 (C=C aromatic).

Bis(2,2,6,6-tetramethyl-4-hydroxy-4-acetyl-1-piperidinoxyl)terephthalylidene (VIII). Compound (VIII) was obtained similarly to (VII) with a 29.2% yield; mp 229-230°C. Found %: N 5.24. mol.wt. 526 (MS). $C_{30}H_{42}N_2O_6$. Calculated %: N 5.32.

2,2,6,6-Tetramethyl-4-hydroxy-4-benzylideneacetylpiperidine (IX). Compound (IX) was obtained from (II) similarly to (VII) with 69.5% yield; mp 120°C (from hexane). Found %: C 75.18; H 9.20; N 4.83. mol. wt. 287 (MS). $C_{18}H_{25}NO_2$. Calculated %: C 75.26; H 8.71; N 4.87. IR spectrum (ν, cm^{-1}): 1620 (C=C), 1680 (C=O conj.).

2,2,6,6-Tetramethyl-5'-phenylpiperidine-4-spiro-2'-(3'-furanone) (X). A mixture of 1 g of (IX) and 2 ml of phosphoric acid was heated at 115-120°C for 4 h. The mixture was then diluted with water, neutralized with potassium carbonate, and extracted with ether. The extract was dried with potassium carbonate, and the solvent was evaporated under vacuum. The residue gave 0.6 g of (X); mp 96°C. Found %: N 4.83. mol.wt. 287 (MS). $C_{18}H_{25}NO_2$. Calculated %: N 4.87. IR spectrum (ν, cm^{-1}): 1750 (C=O).

2,2,6,6-Tetramethyl-5'-phenylpiperidine-4-spiro-2'-(3'-furanone)-1-oxyl (XI). A 0.5-g sample of (X) was dissolved in 10 ml of water, 0.5 g of Na_2WO_4 and 1 ml of 30% hydrogen peroxide were added, and the mixture was left at 20°C for 7 days. The crystals which

separated were filtered off and recrystallized from hexane; mp 118.5-119°C. Found %: N 4.55. mol. wt. 302 (MS). $C_{18}H_{24}NO_3$. Calculated %: N 4.63.

2,2,6,6-Tetramethyl-4-hydroxy-4-benzylideneacetyl-1-piperidinoxyl Oxide (XII). To a solution of 0.8 g of (VII) in 5 ml of methanol at 0°C we simultaneously added drop by drop 0.36 ml of 18% hydrogen peroxide and 0.4 ml of 4 N sodium hydroxide solution. After 2 h we added 10 ml of water. The solution was extracted with ether. The extract was dried with sodium sulfate, the solvent was evaporated under vacuum, and the residue was dissolved in benzene and chromatographed on silica gel LS 100/160 with a 9:1 mixture of chloroform and methanol as eluent. The fraction with R_f 0.72 was collected. The yield of (XII) was 0.6 g (71.4%). Found %: N 4.10. mol.wt. 318 (MS). $C_{18}H_{24}NO_4$. Calculated %: N 4.40. IR spectrum (ν, cm^{-1}): 1696 (C=O).

2,2,6,6-Tetramethyl-4-hydroxymethylol-4-(β-diethylaminopropionyl)-1-piperidinoxyl (XIII). A mixture of 1 g of (III), 0.2 g of trioxane, and 0.7 ml of diethylamine in 25 ml of dioxane was boiled for 10 h. The excess of diethylamine was evaporated under vacuum, the mixture was diluted with 50 ml of water and acidified to pH 3 with 10% hydrochloric acid, and the initial compound (III) was extracted with ether. The water—dioxane fraction was then made alkaline to pH 9 with potassium carbonate, and the Mannich base was extracted with ether. The extract was dried with sodium sulfate, the ether was distilled, the residue was dissolved in benzene, and the solution was chromatographed on silica gel LS 100/60 with a 9:1 mixture of chloroform and methanol as eluent. The fraction with R_f 0.1 was collected. A 0.2-g yield (15%) of (XIII) was obtained in the form of a red oil. Found %: C 62.41; H 9.97; N 8.47. mol.wt. 329 (MS). $C_{17}H_{33}N_2O_4$. Calculated %: C 62.00; H 10.00; N 8.51.

2,2,6,6-Tetramethyl-4-hydroxy-4-(β-diethylaminopropionyl)-1-piperidinoxyl (XIV). Compound (XIII) was boiled in dilute hydrochloric acid at pH 4 for 1 h. The mixture was made alkaline to pH 9 with potassium carbonate and extracted with benzene. The extract was dried with sodium sulfate, and the benzene was evaporated under vacuum. The residue gave 0.15 g (82.4%) of (XIV). Found %: C 64.50; H 10.22; N 9.44. mol.wt. 299 (MS). $C_{16}H_{31}N_2O_3$. Calculated %: C 64.21; H 10.36; N 9.36.

Complexes of 2,2,6,6-Tetramethyl-4-hydroxy-4-trifluoroacetoacetyl-1-piperidinoxyl (L) with Co^{2+} and Cu^{2+} (XVI). To a mixture of 0.6532 g of ethyl trifluoroacetate, 0.105 g of sodium in 0.3 ml of absolute ethanol, and 10 ml of absolute ether at 20°C we added drop by drop 1 g of (III) in 20 ml of absolute ether. The mixture was boiled for 5 h, and a solution of 0.5 g of $CoCl_2 \cdot 6H_2O$ in 20 ml of absolute ethanol was then added. A 200-ml portion of water was added, the mixture was extracted with ether, and the extract was dried with sodium sulfate. The ether was evaporated under vacuum. The residue was dissolved in benzene and chromatographed on a column of silica gel LS-100/160 with a 9:1 mixture of chloroform and methanol as eluent. A 0.5-g sample of $Co(L)_2$ was obtained; decomp. p. 200°C. Found %: C 46.63; H 5.21; N 4.20; F 16.53; Co 8.41. $(C_{13}H_{18}NO_4F_3)_2Co$. Calculated %: C 46.15; H 5.33; N 4.14; F 16.86; Co 8.55. IR spectrum (ν, cm^{-1}): 1545 (C—O—Co^{2+} and C=O...Co^{2+}), 1520 (C=C conj.).

The complex $Cu(L)_2$ was obtained similarly; decomp. p. 200°C. Found %: C 46.03; H 5.50; N 3.94; F 16.54; Cu 9.61. $(C_{13}H_{18}NO_4F_3)_2Cu$. Calculated %: C 45.78; H 5.28; N 4.10; F 16.72; Cu 9.32. IR spectrum (ν, cm^{-1}): 1545 (C—O—Cu^{2+} and C=O...Cu^{2+}), 1525 (C=C conj.).

2,2,6,6-Tetramethyl-4-ethynyl-Δ^3-dihydropiperidine (XVII). A mixture of 5 g of (I) and 2.6 ml of phosphorus oxychloride in 20 ml of dry benzene was boiled for 1.5 h. The mixture was then added to water, and the benzene layer was separated and washed twice with 10% hydrochloric acid. The aqueous extracts were combined and neutralized with potassium carbonate, extracted with benzene, and dried with sodium sulfate. The benzene was distilled under vacuum, and the residue was recrystallized from hexane. A 2.5-g yield (55%) of (XVII) was obtained; mp 76°C. Found %: C 80.91; H 10.52; N 8.75. mol.wt. 163 (MS). $C_{11}H_{17}N$. Calculated %: C 80.98; H 10.43; N 8.59. IR spectrum (ν, cm^{-1}): 2120 (C≡C conj.).

2,2,6,6-Tetramethyl-4-acetyl-Δ^3-dehydropiperidine (XVIII). Compound (XVIII) was obtained similarly to (II) with a 69.1% yield; bp 61-62°C (0.02 mm Hg). Found %: C 72.79; H 10.55; N 7.70. mol.wt. 181 (MS). $C_{11}H_{19}NO$. Calculated %: C 72.92; H 10.49; N 7.73. IR spectrum (ν, cm^{-1}): 1680 (C=O conj.), 3340 (N—H).

2,2,6,6-Tetramethyl-4-acetyl-Δ^3-dehydro-1-piperidinoxyl (XIX). To a solution of 2 g of (XVIII) in 50 ml of 50% methanol we added 0.5 g of Na_2WO_4 and 2 ml of 30% hydrogen peroxide.

After four days the solution was saturated with potassium carbonate, extracted with ether, and dried with sodium sulfate. The ether was distilled under vacuum, and the residue was purified on a column of silica gel LS 100/160. The fraction with R_f 0.5 was eluted with chloroform. A 2-g yield (92.2%) of (XIX) was obtained; bp 124-126°C (13 mm Hg). Found %: C 66.98; H 9.18; N 7.01. mol.wt. 196 (MS). $C_{11}H_{18}NO_2$. Calculated %: C 67.34; H 9.13; N 7.15. IR spectrum (ν, cm^{-1}): 1680 (C=O conj.).

2,2,6,6-Tetramethyl-4-(β-diethylaminopropionyl)-Δ^3-dehydro-1-piperidinoxyl (XX). Compound (XX) was obtained similarly to (XIII) with a 17.5% yield; bp 128°C (0.05 mm Hg). Found %: C 68.51; H 10.22; N 9.57. mol.wt. 281 (MS). $C_{16}H_{29}N_2O_2$. Calculated %: C 68.32; H 10.32; N 9.96.

2,2,6,6-Tetramethyl-4-trifluoroacetoacetyl-Δ^3-dehydro-1-piperidinoxyl (XXI). Compound (XXI) was obtained similarly to (XV). The mixture was diluted with water and extracted with ether. The extract was dried with sodium sulfate, and the ether was distilled under vacuum. The residue was dissolved in benzene and chromatographed on a column of silica gel LS 100/160 with a 9:1 mixture of chloroform and methanol as eluent. The fraction with R_f 0.33 was collected. From 0.5 g of (XIX) we obtained 0.33 g (44.5%) of (XX); decomp. p. 75-80°C. Found %: C 53.31; H 5.50; N 5.01; F 19.14. mol.wt. 292 (MS). $C_{13}H_{17}NF_3O_3$. Calculated %: C 53.42; H 5.82; N 4.79; F 19.58. IR spectrum (ν, cm^{-1}): 1680 (C=O conj.), 1630 (C=O...H—O↔C=O—H...O).

Complexes of the β-Diketone (XXI) with Co^{2+} and Cu^{2+} (XXII). To 0.5 g of (XXI) in 20 ml of ethanol we added 0.23 g of $CoCl_2 \cdot 6H_2O$ in 10 ml of ethanol. The mixture was diluted to 100 ml with water and extracted with ether. The extract was dried with sodium sulfate, the ether was distilled under vacuum, and the residue was chromatographed on silica gel LS 100/160 with chloroform as eluent. A 0.25-g yield (23%) of the cobalt complex was obtained; decomp. p. 200°C. Found %: C 48.35; H 4.75; N 4.53; F 17.38; Co 8.95. $(C_{13}H_{16}NF_3O_3)_2Co$. Calculated %: C 48.65; H 4.99; N 4.37; F 17.45; Co 9.08. IR spectrum (ν, cm^{-1}): 1540 (C—O—Co^{2+} and C=O...Co^{2+}), 1505 (C=C).

The copper complex was obtained similarly with a 28% yield; decomp. p. 200°C. Found %: C 47.95; H 5.21; N 4.51; F 17.31; Cu 9.75. $(C_{13}H_{16}NF_3O_3)_2Cu$. Calculated %: C 48.31; H 5.09; N 4.34; F 17.63; Cu 9.83. IR spectrum (ν, cm^{-1}): 1540 (C—O—Cu^{2+} and C=O...Cu^{2+}), 1515 (C=C).

4-Vinyl-4-hydroxy-2,2,6,6-tetramethylpiperidine (XXIII). An 18.1-g sample of compound (I) in 150 ml of methanol was hydrogenated over Lindlar's catalyst at 20°C until 0.1 mole of hydrogen had been absorbed. The catalyst was filtered off, the solvent was evaporated under vacuum, and the residue was recrystallized from hexane. An 18-g yield (98.4%) of (XXIII) was obtained in the form of white crystals; mp 55-56°C. Found %: C 72.21; H 11.64; N 7.43. mol.wt. 183 (MS). $C_{11}H_{21}NO$. Calculated %: C 72.13; H 11.48; N 7.65. IR spectrum (ν, cm^{-1}): 1645 (C=C), 1310 (C—O of tertiary alcohol).

4-Vinyl-4-hydroxy-2,2,6,6-tetramethyl-1-piperidinoxyl (XXIV). A mixture of 5 g of (XXIII), 0.5 g of Na_2WO_4, 0.5 g of Trilon B, 15 ml of 30% hydrogen peroxide, and 80 ml of methanol was left for 10 days. The precipitate was filtered off, and the methanol was distilled under vacuum. The residue was diluted with water and extracted with ether. The extract was dried with sodium sulfate. After drying, the filtrate was evaporated under vacuum, and the residue was chromatographed on aluminum oxide of medium activity with chloroform as eluent, and the fraction with R_f 0.48 was collected. A 4.65-g yield (86.1%) of (XXIV) was obtained in the form of red crystals; mp 83-84°C (from hexane). Found %: C 66.71; H 10.21; N 6.95. mol.wt. 198 (MS). $C_{11}H_{20}NO_2$. Calculated %: C 66.67; H 10.10; N 7.07. IR spectrum (ν, cm^{-1}): 1640 (C=C).

4-Vinyl-2,2,6,6-tetramethyl-Δ^3-dehydropiperidine (XXV). A mixture of 5 g of (XXIII), 3 ml of phosphorus oxychloride, and 20 ml of dry benzene was boiled for 3 h, cooled, and added to water. The benzene layer was removed and washed with 10% hydrochloric acid. The combined aqueous extracts were made alkaline with potassium carbonate and extracted with ether. The extract was dried with sodium sulfate and evaporated under vacuum. To the residue we added hydroquinone. The mixture was distilled under vacuum, and 2.1 g (46.56%) of a light-yellow liquid was obtained. It polymerized on storage; bp 90-92°C (1 mm Hg); d_4^{20} 0.9254, n_D^{20} 1.4580. Found %: C 80.23; H 11.52; N 8.29. mol.wt. 165 (MS). $C_{11}H_{19}N$. Calculated %: C 80.00; H 11.52; N 8.48. IR spectrum (ν, cm^{-1}): 1610 (C=C conj.), 3470 (N—H).

4-Vinyl-2,2,6,6-tetramethyl-Δ^3-dehydro-1-piperidinoxyl (XXVI). a. A mixture of 0.5 g of (XXIV), 2.5 ml of pyridine, and 0.2 ml of phosphorus oxychloride was left overnight, added to water, and extracted with ether. The extract was washed repeatedly with dilute hydrochloric acid (pH 3) and with water, dried with sodium sulfate, and evaporated under vacuum. The residue was chromatographed on aluminum oxide of medium activity with chloroform as eluent, and the fraction with R_f 0.84 was collected. A 141-mg yield (31.2%) of (XXVI) was obtained in the form of a red liquid; d_4^{20} 0.9363, n_D^{20} 1.4789. Found %: C 73.08; H 10.08; N 7.78. mol. wt. 180 (MS). $C_{11}H_{18}NO$. Calculated %: C 73.33; H 10.00; N 7.78. IR spectrum (ν, cm^{-1}): 1610 (C=C conj.).

b. A mixture of 1 g of (XXV), 0.3 g of Na_2WO_4, 30 ml of methanol, and 5 ml of hydrogen peroxide was left to stand for 5 days. It was then treated as in the case of (XXIV). A 0.28-g yield (25.7%) of a compound identical with that obtained in the previous experiment was obtained.

4-Ethynyl-2,2,6,6-tetramethyl-Δ^3-dihydro-1-piperidinoxyl (XXVII). A mixture of 0.5 g of (XVII), 0.2 g of Na_2WO_4, 10 ml of methanol, and 3 ml of 30% hydrogen peroxide was left for 2 days. After the treatment described in the synthesis of (XXIV) we obtained 0.44 g (80%) of (XXVII) in the form of orange crystals; mp 47°C (from hexane). Found %: C 74.13; H 9.12; N 7.82. mol.wt. 178 (MS). $C_{11}H_{16}NO$. Calculated %: C 74.15; H 8.98; N 7.86.

4-Vinyl-4-hydroxy-2,2,6,6-tetramethyl-1-piperidinoxyl Oxide (XXVIII). To a solution of 0.5 g of (XXIV) in 10 ml of chloroform, cooled to 0°C, we added dropwise with stirring a solution of 1 g of m-chloroperbenzoic acid in 30 ml of chloroform. The mixture was kept at 20°C for 20 h, washed with a 40% solution of sodium bicarbonate and with water, and dried with sodium sulfate. The residue after evaporation of the solvent was chromatographed on silica gel LS 100/160 with a 10:1 mixture of chloroform and methanol as eluent. The fraction with R_f 0.5 was collected. A 0.32-g yield (40.5%) of (XXVIII) was obtained in the form of light-orange crystals; mp 76-77°C (from hexane). Found %: C 61.84; H 9.68; N 6.35. mol. wt. 214 (MS). $C_{11}H_{20}NO_3$. Calculated %: C 61.68; H 9.35; N 6.54.

4-Vinyl-2,2,6,6-tetramethyl-Δ^3-dehydro-1-piperidinoxyl Oxide (XXIX). Compound (XXIX) was obtained similarly to compound (XXVIII). After chromatography on silica gel LS100/160 with a 10:1 mixture of chloroform and methanol as eluent we obtained (XXIX) in the form of a red liquid with R_f 0.66. The yield was 55%; d_4^{20} 0.9282, n_D^{20} 1.4852. Found %: C 67.64; H 9.04; N 7.07. mol. wt. 196 (MS). $C_{11}H_{18}NO_2$. Calculated %: C 67.35; H 9.18; N 7.14.

The Adduct of Maleic Anhydride with 4-Vinyl-2,2,6,6-tetramethyl-Δ^3-dehydro-1-piperidinoxyl (XXX). The precipitate which separated from a solution of 180 g of (XXVI) and 98 g of maleic anhydride in 3 ml of dry benzene after standing for a month was filtered off and washed with hexane. A 220-mg yield (79.1%) of (XXX) was obtained in the form of a light-brown powder; mp 95°C (decomp.). Found %: C 64.51; H 7.29; N 5.02. $C_{15}H_{20}NO_4$. Calculated %: C 64.75; H 7.19; N 5.05. IR spectrum (ν, cm^{-1}): 1725 (C=O).

The Adduct (XXXI) of p-Benzoquinone with (XXVI). The adduct was obtained similarly to (XXX) from 180 mg of (XXVI) and 108 mg of benzoquinone in the form of a dark-brown powder; mp 155°C (decomp.). The yield of the adduct was 240 mg (83.3%). Found %: C 70.47; H 7.82; N 4.74. $C_{17}H_{22}NO_3$. Calculated %: C 70.83; H 7.64; N 4.86. IR spectrum (ν, cm^{-1}): 1650 (C=O quinone).

CONCLUSIONS

1. Stable nitroxyl radical derivatives of 2,2,6,6-tetramethylpiperidine containing functional groups were synthesized: paramagnetic trifluoro-β-diketones, α-hydroxy and α-keto oxides, Mannich bases, tetrahydrofuranones, unsaturated ketones, vinylacetylenic and divinyl monomers, certain diene synthesis adducts, and chelate complexes of Cu(II) and Co(II) with paramagnetic organic ligands.

2. The possibility of the participation of stable nitroxyl radicals in the Mannich, Claisen, Prilezhaev, and Weitz and Scheffer reactions was demonstrated for the first time.

LITERATURE CITED

1. A. B. Shapiro and É. G. Rozantsev, Inventor's Certificate No. 435236 (1973); Byull. Izobr., No. 25 (1974).
2. I. N. Nazarov, Collected Works [in Russian], Izd. Akad. Nauk SSSR (1961), pp. 65, 311.

3. G. I. Likhtenshtein, The Spin Label Method in Molecular Biology [in Russian], Nauka (1974).
4. S. V. Larionov, V. I. Ovcharenko, R. A. Sadykov, and L. B. Volodarskii, Izv. Akad. Nauk SSSR, Ser. Khim., 1975, 1922.
5. A. A. Medzhidov, A. B. Shapiro, P. Sh. Mamedova, A. M. Musaev, and É. G. Rozantsev, Izv. Akad. Nauk SSSR, Ser. Khim., 1977, 538.
6. A. B. Shapiro, V. V. Pavlikov, and É. G. Rozantsev, Dokl. Akad. Nauk SSSR, 232, 398 (1977).
7. I. N. Nazarov, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk, 1940, 203.
8. E. Weitz and A. Scheffer, Berichte, 54, 2327 (1921).
9. A. B. Shapiro, L. N. Skripnichenko, V. M. Chumakov, V. V. Pavlikov, and É. G. Rozantsev, Bioorg. Khim., 3, 707 (1977).

REACTION OF α,α,ω-TRIHYDROPERFLUOROALKANOLS WITH PHOSPHORUS TRICHLORIDE

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The only known example of the interaction of α,α,ω-trihydroperfluoroalkanes with PCl_3 is 1,1,3-trihydroperfluoropropanol (I). In [1], bis(1,1,3-trihydroperfluoropropyl) chlorophosphite was obtained in a low yield; it readily disproportionates upon standing, but in the presence of diethylaniline the corresponding trialkyl phosphite is obtained. Prons, Grinblat, and Klebanskii [2] showed by GLC that when (I) is added to PCl_3 only dialkyl chlorophosphite and trialkyl phosphite are formed in a ratio 1:8 to 1:10.

We attempted to make a more detailed study of the character of the interaction of α,α,ω-trihydroperfluoroalkanols with PCl_3. It has been shown that the direction of the reactions of (I), 1,1,5-trihydroperfluoropentanol (II), and 1,1,7-trihydroperfluoroheptanol (III) with PCl_3 is determined by the reagent ratio and the temperature conditions. The characteristic property of these reactions is the absence of significant exo effects, which excludes the necessity for using solvents.

In a mixture of equimolar quantities of (I), (II), or (III) with PCl_3 an equilibrium is established. In an equilibrium mixture up to 80°C the main products (according to GLC data, up to 80-85°C) are the following alkyl dichlorophosphites:

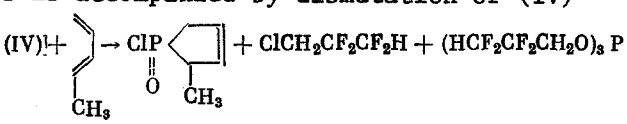
$$H(CF_2)_nCH_2OH + PCl_3 \rightarrow H(CF_2)_nCH_2OPCl_2$$
$$n = 2\ (IV),\ 4\ (V),\ 6\ (VI)$$

Above 80°C in vacuo the equilibrium is shifted in the direction of trialkyl phosphite formation. Therefore (IV), (V), and (VI) can be isolated individually by fractionation in vacuo at ≤ 60-80°C. The compounds are relatively stable when stored. Under mild conditions (0-5°C) (IV) is smoothly oxidized by N_2O_4 into the corresponding alkyl dichlorophosphate (VII)

$$(VI) + N_2O_4 \rightarrow HCF_2CF_2CH_2OP(=O)Cl_2 \quad (VII)$$

It is interesting that the reaction of (IV) takes place with piperylene. Mixing of the reagents is accompanied by evolution of heat, and at 20°C only disproportation of the original (IV) occurs. The McCormack condensation takes place only at a low rate at 60°C, and at a marked rate at ≥ 100°C.

In any case the process is accompanied by dismutation of (IV)



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