HALOGEN-CONTAINING NITROXYL RADICALS.

COMMUNICATION 4.* THE SYNTHESIS AND REACTIONS OF 3-BROMO-4-DIAZOACETYL-2,2,5,5-TETRAMETHYL-Δ^3-PYRROLIN-1-OXYL

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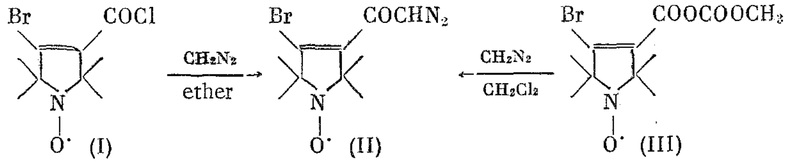
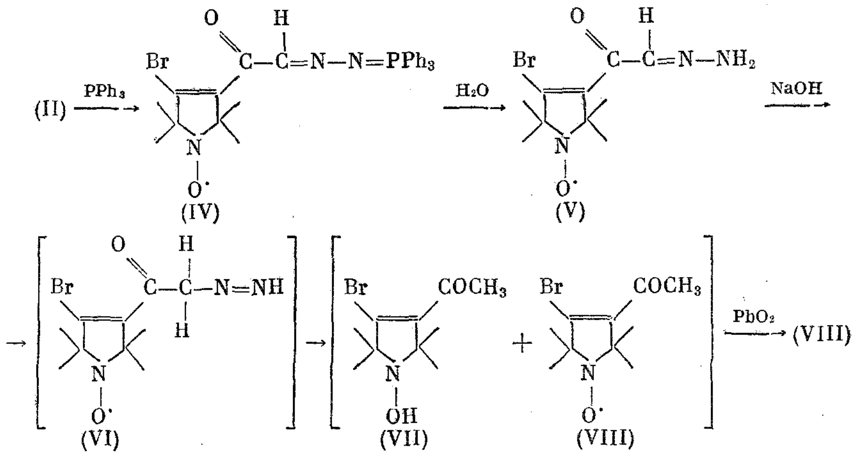
In the previous work, we obtained a series of carbonyl-containing bromopyrroline nitroxyl radicals which are derivatives of 3-bromo-4-carboxy-2,2,5,5-tetramethyl-Δ^3-pyrrolin-1-oxyl and demonstrated the inertness of the bromine and diminished reactivity of the carbonyl group of these compounds in nucleophilic substitution reactions [1]. In the present work, we extended our study of the chemical transformations of this new series of nitroxyl radicals.

Treatment of acid chloride (I) with an ethereal solution of diazomethane in the presence of triethylamines gives good yields of the stable diazoketone (II)



Anhydride (III) [1] reacts extremely slowly with diazomethane in ether. The reaction rate is significantly enhanced by using a solution of diazomethane in methylene chloride, which permits the facile preparation of diazoketone (II) from anhydride (III) in good yield.

Ketone (VIII) was synthesized from (II) by the method of Bestian [2] through the following scheme:



Diazoketone (II) reacts with triphenylphosphine in ether to give phosphazine (IV) whose hydrolysis yields hydrazone (V). The action of dilute aq. NaOH on (V) gives the intermediate formation of diimide (VI) [3] which partially reduces the nitroxyl radical to hydroxylamine (VII). Thus, ketone (VIII) was separated prior to complete oxidation of the reaction mixture by lead dioxide.

The action of concentrated HCl on an ethereal solution of (II) yields chloroketone (IX) which was used for the synthesis of a potential nitroxyl monomer [epoxide (XI)] by the scheme

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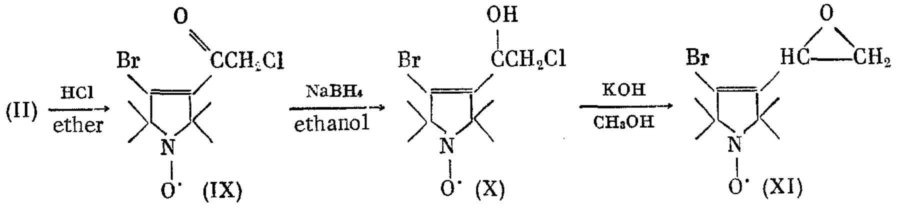
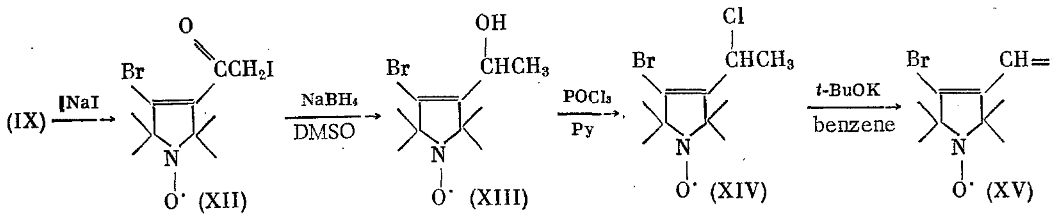
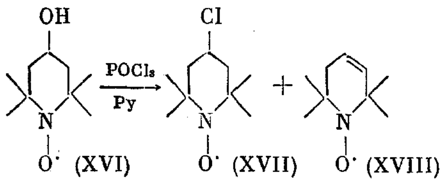


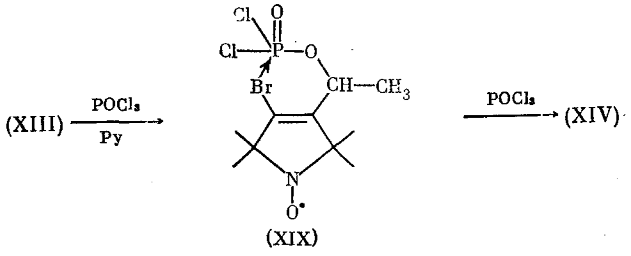
Iodoketone (XII) obtained from chloroketone (IX) was reduced by NaBH$_4$ in DMSO by the method of Hutchins et al. [4] to give secondary alcohol (XIII). The reduction of ketone (VIII) by NaBH$_4$ in ethanol gives the same alcohol



The treatment of alcohol (XIII) by POCl$_3$ in pyridine mainly gives chloride (XIV) and only a small amount of the expected olefin (XV) (the ratio of these products is 95:5) [5]. Chloride (XVII) and olefin (XVIII) are obtained in 14:86 ratio under the same conditions from alcohol (XVI).

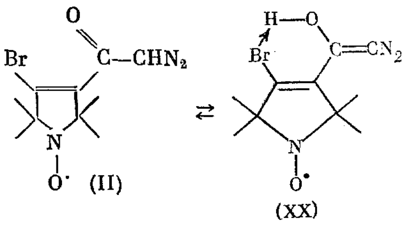


The transformation of (XIV) is apparently a consequence of an intramolecular interaction of the bromine and phosphorus atoms in intermediate ester (XIX) leading to a decrease in the electron-withdrawing properties of the dichlorophosphate group and hindrance to the elimination reaction



The reaction of ester (XIX) and POCl$_3$ which is found partially as the salt $(C_5H_5N\cdot POCl_2)^+Cl^-$ which is more reactive in nucleophilic substitution reactions in the presence of pyridine [6] leads to the formation of (XIV).

We should note that the IR spectrum of diazoketone (II) has a weak band in the OH group region at 3140 cm^{-1} which is usually not found for diazoketones and may be explained by the presence of the enol form of the diazoketone (XX) stabilized by intermolecular hydrogen bonding



Treatment of chloride (XIV) by t-BuOK in benzene in the presence of 18-crown-6-ether phase transfer catalyst leads to olefin (XV).

EXPERIMENTAL

Samples of starting 3-bromo-4-chloroformyl-2,2,5,5-tetramethyl-Δ^3-pyrrolin-1-oxyl (I) and the mixed anhydride of 1-oxyl-3-bromo-2,2,5,5-tetramethyl-Δ^3-pyrroline-4-carboxylic and methoxycarbonic acids (II) were obtained by methods given in our previous work [1]. The IR spectra were taken on a UR-20 spectrometer in KBr pellets. The mass spectra were taken on a RMU-6D mass spectrometer. The ESR spectra were recorded on an EPRB-IKhF spectrometer in dilute toluene solution at 25°C. The measurement errors are $a_N = \pm 0.01$ mT and $g = \pm 0.0001$. The gas-liquid chromatographic analysis was carried out on a Khrom-4 chromatograph using a stainless steel column packed with 5% SE-30 100-120-μm Chesasorb, flame ionization detector, isothermal mode, and 25 ml/min nitrogen carrier gas flow rate. The product composition was found assuming identical sensitivity coefficients of the flame ionization detector for the compounds analyzed relative to the areas of the peaks of the corresponding components; the measurement error was ±5%.

3-Bromo-4-diazoacetyl-2,2,5,5-Δ^3-pyrrolin-1-oxyl (II). A sample of 0.01 mole triethylamine and a solution of 0.01 mole acid chloride (I) in 50 ml ether were added consecutively over 15 min with stirring and ice cooling to a dry solution of diazomethane in 50 ml ether obtained from the reaction of 0.025 mole N-nitromethylurea with 10 ml 40% aq. KOH. The mixture was stirred with ice cooling for 2 h. The precipitate was filtered off and the filtrate was evaporated in vacuum and subjected to chromatography on a 450 × 16-mm column packed with silica gel LS 40/100.

The first colored band was eluted with 1:5 ether–hexane. Removal of the solvent gave 0.27 g (9.1%) chloroketone (IX) as yellow crystals with mp 90-91°C (from hexane). Found: C, 40.70; H, 4.79; N, 4.82%, mol. mass 294 (M^+), 296 (M^+), 298 (M^+), mass spectroscopically. Calculated for $C_{10}H_{14}BrClNO_2$: C, 40.63; H, 4.77; N, 4.75%, mol. mass 295.59. IR spectrum (ν, cm^{-1}): 1590 (C=C), 1690 (C=O). The ESR spectrum was a triplet with $a_N = 1.34$ mT and $g = 2.0055$.

The second colored band was eluted with 1:1 ether–hexane. Removal of the solvent gave 2.19 g (80.3%) (II) as yellow crystals with mp 86-87°C (from hexane). Found: C, 41.77; H, 4.53; N, 14.69%, mol. mass 286 (M^+), 288 (M^+). Calculated for $C_{10}H_{13}BrN_3O_2$: C, 41.83; H, 4.56; N, 14.63%, mol. mass 287.140. IR spectrum (ν, cm^{-1}): 1590 (C=C), 1600 (C=O), 2120 (CHN_2), 3140 (OH). The ESR spectrum was a triplet with $a_N = 1.35$ mT and $g = 2.0057$.

b) Anhydride (III) was added in batches with stirring and ice cooling to a dry solution of diazomethane in 80 ml CH_2Cl_2 obtained from 0.05 mole N-nitrosomethyurea. Then, the mixture was stirred for 4 h at ∿20°C. The solvent was removed in vacuum and the residue was subjected to chromatography on a 300 × 16-mm column packed with LS 40/100 silica gel. The first colored band was eluted with 1:5 ether–hexane. Removal of the solvent gave 0.20 g (7%) 3-bromo-4-carbomethoxy-2,2,5,5-tetramethyl-Δ^3-pyrrolin-1-oxyl with mp 130-131°C (from hexane). The mixed melting point with an authentic sample [7] was not depressed. The IR spectra of both samples were completely identical. The second colored band was eluted with 1:1 ether–hexane. Removal of the solvent gave 2.5 g (87%) (II).

3-Bromo-4-(β-triphenylphosphazinoglyoxaline)-2,2,5,5-tetramethyl-Δ^3-pyrrolin-1-oxyl (IV). A sample of 1.44 g (0.005 mole) diazoketone (II) was added in one batch with stirring and ice cooling to a solution of 7.5 mmoles triphenylphosphine in 12 ml dry ether. The mixture was stirred for 30 min with ice cooling. The crystals formed were filtered off and washed with dry ether. Drying yielded 2.64 g (96.4%) (IV) as pink crystals with mp 153-154°C (decomp.). Found: C, 61.35; H, 5.19; N, 7.80%. Calculated for $C_{28}H_{28}BrN_3PO_2$: C, 61.21; H, 5.14; N, 7.65%, mol. mass 549.40. IR spectrum (ν, cm^{-1}): 1500 (phenyl C=C), 1590, 1600, 3060 (phenyl CH). The ESR spectrum was a triplet with $a_N = 1.39$ mT and $g = 2.0057$.

3-Bromo-4-(β-hydrazonoglyoxalyl)-2,2,5,5-tetramethyl-Δ^3-pyrrolin-1-oxyl (V). A suspension of 0.005 mole phosphazine (IV) in a mixture of 4 ml water and 16 ml methanol was heated at reflux for 1.5 h. The precipitate was fully dissolved. Methanol was removed in vacuum. The residue was extracted with benzene. The extract was washed with brine and dried over $MgSO_4$. After removal of the solvent, the residue was subjected to chromatography on a 500 × 16-mm column packed with LS 40/100 silica gel using 2:1 ether–hexane as the eluent. The first colored band was separated. Removal of the solvent and recrystallization of the residue from 1:2 chloroform–hexane yielded 0.88 g (61%) (V) as light yellow crytals. This compound does not have a distinct melting point; it melts in the range from 130° to 140°C (depending on the heating rate) and decomposes in the presence of traces of alkali. Found: C, 41.42; H, 5.27;

N, 14.50%, mol. mass 288 (M^+), 290 (M^+). Calculated for $C_{10}H_{15}BrN_3O_2$: C, 41.53; H, 5.23; N, 14.50%, mol. mass 289.16. IR spectrum (ν, cm^{-1}): 1570, 1620, 3200, and 3300 (NH_2). The ESR spectrum is a triplet with a_N = 1.39 mT and g = 2.0057.

3-Bromo-4-acetyl-2,2,5,5-tetramethyl-Δ^3-pyrrolin-1-oxyl (VIII). A suspension of 0.005 mole phosphazine (IV) in a mixture of 4 ml water and 16 ml methanol was heated at reflux for 2. Then, 2 ml 1 N NaOH was added and the mixture was heated at reflux for an additional 1 h. Gas liberation was noted and the mixture became dark red. Methanol was evaporated in vacuum and the residue was extracted with benzene. The benzene extract was washed with aq. NaCl. The extract was dried over $MgSO_4$ and reduced to 30 ml. A sample of 0.026 mole PbO_2 was added and the mixture was stirred for 24 h. Then, the precipitate was filtered off and the solvent was evaporated in vacuum. The residue was subjected to chromatography on a 200 × 16-mm column packed with LS 40/100 silica gel using 1:2 ether—hexane as eluent. The first colored band was separated. Solvent removal gave 0.63 g (48%) (VIII) as yellow crystals with mp 71.5-72.5°C (from pentane). Found: C, 46.09; H, 5.68; N, 5.45%, mol. mass 260 (M^+), 262 (M^+). Calculated for $C_{10}H_{15}BrNO_2$: C, 45.99; H, 5.79; N, 5.36%, mol. mass 261.144. IR spectrum (ν, cm^{-1}): 1590 (C=C), 1670 (C=O). The ESR spectrum was a triplet with a_N = 1.32 mT and g = 2.0056.

3-Bromo-4-chloroacetyl-2,2,5,5-tetramethyl-Δ^3-pyrrolin-1-oxyl (IX). A sample of 3.5 ml (0.04 mole) concentrated HCl (d = 1.185) was added dropwise over 5 min with rapid stirring and ice cooling to a solution of 0.01 mole diazoketone (II) in 100 ml ether. The mixture was stirred for an additional 30 min with ice cooling. Then, a sample of 1 g NaCl was added and the mixture was stirred for 20 min. A sample of 20 ml saturated aq. $NaHCO_3$ was added and the mixture was stirred for 10 min. The organic layer was separated, washed with water, and dried over $MgSO_4$. Removal of the solvent gave 2.87 g (97%) pure (X) with mp 90-91°C (from hexane). All the characteristics of the product were identical to those of the compound described above.

3-Bromo-4-(1-hydroxy-2-chloroethyl)-2,2,5,5-tetramethyl-Δ^3-pyrrolin-1-oxyl (X). A sample of 0.00375 mole $NaBH_4$ was added in portions over 5 min to a suspension of 0.05 mole chloroketone (IX) in 20 ml ethanol with stirring at from —15° to —20°C. The mixture was stirred for an additional 15 min at this temperature. Then, the mixture was placed on an ice bath and stirred for 30 min. A sample of 0.01 mole NH_4Cl was added and the solvent was removed in vacuum. A sample of 10 ml water was added to the residue and the mixture was extracted with ether. The ethereal extract was washed with aq. NaCl and dried over $MgSO_4$. The solvent was evaporated. Recrystallization from hexane gave 1.27 g (85.5%) (X) as greenish yellow crystals with mp 87-88°C (from hexane). Found: C, 40.48; H, 5.52; N, 4.80%, mol. mass 296 (M^+), 298 (M^+), 300 (M^+). Calculated for $C_{10}H_{16}BrClNO_2$: C, 40.35; H, 5.42; N, 4.71%, mol. mass 297.611. IR spectrum (ν, cm^{-1}): 1640 (C=C), 3300-3400 (OH). The ESR spectrum was a triplet with a_N = 1.40 mT and g = 2.0057.

3-Bromo-4-epoxy-2,2,5,5-tetramethyl-Δ^3-pyrrolin-1-oxyl (XI). A solution of 0.02 mole KOH in 2.5 ml water was added with stirring at ∿20°C to a solution of 5 mmoles chlorohydrin (X) in 10 ml methanol. The mixture was stirred for 1 h and then poured into 50 ml water and extracted with ether. The ethereal extract was washed with aq. NaCl, dried over $MgSO_4$, and treated with decolorizing activated charcoal. Removal of the solvent gave 1.3 g (98%) pure (XI) as yellow crystals with mp 77-78°C (sublimate). Found: C, 45.94; H, 5.82; N, 5.42%, mol. mass 260 (M^+), 262 (M^+). Calculated for $C_{10}H_{15}BrNO_2$: C, 45.99; H, 5.79; N, 5.36%, mol. mass 261.144. IR spectrum (ν, cm^{-1}): 1650 (C=C), 3070 (epoxide CH). The ESR spectrum was a triplet with a_N = 1.32 mT and g = 2.0057.

3-Bromo-4-iodoacetyl-2,2,5,5-tetramethyl-Δ^3-pyrrolin-1-oxyl (XII). A sample of 5 mmoles chloroketone was added with stirring at ∿20°C to a solution of 0.01 mole NaI in 20 ml dry acetone and the mixture was stirred for 1 h. The solvent was removed in vacuum. A sample of 20 ml 10% aq. $Na_2S_2O_3$ was added to the residue and the mixture was extracted with ether. The ethereal extract was washed with water and aq. NaCl and dried over $MgSO_4$. Removal of the solvent and recrystallization from hexane gave 1.9 g (98%) (XII) as orange-yellow crystals with mp 93-94°C (from hexane). Found: C, 31.17; H, 3.72; N, 3.68%, mol. mass 386 (M^+), 388 (M^+). Calculated for $C_{10}H_{14}NBrIO_2$: C, 31.03; H, 3.65; N, 3.62%, mol. mass 387.044. IR spectrum (ν, cm^{-1}): 1600 (C=C), 1665 (C=O). The ESR spectrum was a triplet with a_N = 1.34 mT and g = 2.0055.

3-Bromo-4-(α-hydroxyethyl)-2,2,5,5-tetramethyl-Δ^3-pyrrolin-1-oxyl (XIII). a) A sample of of 0.04 $NaBH_4$ was added in portions over 5 min at ∿20°C with stirring to a solution of 0.01

mole iodoketone (XII) in dry DMSO. The mixture was then heated for 1 h at 90-95°C. After cooling to ∿20°C, a solution of 0.04 mole NH_4Cl in 20 ml water was added and the mixture was poured into 200 ml aq. NaCl and extracted with $CHCl_3$. This extract was washed with aq. NaCl and dried over $MgSO_4$. The solvent was removed in vacuum. Benzene was added and evaporated at 30-35°C bath temperature. The residue was subjected to chromatography on a 250 × 16-mm column packed with silica gel LS 40/100 using 2:1 ether–hexane. The first colored band was taken which, after removal of the solvent, gave 2.28 g (86.5%) (XIII) as yellow crystals with mp 90-91°C (from hexane). Found: C, 45.53; H, 6.61; N, 5.44, mol. mass 262 (M^+), 264 (M^+). Calculated for $C_{10}H_{17}BrNO_2$: C, 45.64; H, 6.51; N, 5.32%, mol. mass 263.164. IR spectrum (ν, cm^{-1}): 1650 (C=C), 3440 (OH). The ESR spectrum was a triplet with a_N = 1.40 mT and g = 2.0057.

b) A sample of 0.02 mole $NaBH_4$ was added in portions over 5 min with stirring and ice cooling to a solution of 0.01 mole ketone (VIII) in 40 ml ethanol. The mixture was then stirred for 2 h at ∿20°C. The solvent was removed in vacuum. A sample of 50 ml aq. NaCl was added and the mixture was extracted with chloroform. The extract was washed with aq. NaCl and dried over $MgSO_4$. The solvent was removed. Recrystallization from hexane gave 2.36 g (90%) (XIII).

3-Bromo-4-(α-chloroethyl)-2,2,5,5-tetramethyl-Δ^3-pyrrolin-1-oxyl (XIV). A solution of 6.25 mmoles $POCl_3$ in 5 ml pyridine was added dropwise over 5 min with stirring and ice cooling to a solution of 5 mmoles alcohol (XIII) in 5 ml dry pyridine and maintained at ∿20°C for 40 h. The mixture was then poured into 50 ml water and extracted with ether. The ethereal extract was washed with 5% HCl, water, and aq. $NaHCO_3$ and dried over $MgSO_4$. The solution was treated with decolorizing activated charcoal. Removal of the solvent gave 1 g of a crystalline residue which was shown by gas-liquid chromatography to consist of a 95:5 mixture of chloride (XIV) and olefin (XV). Recrystallization from hexane gave 0.96 g (68%) (XIV) as yellow crystals with mp 69.5-70°C (from hexane). Found: C, 42.60; H, 5.60; N, 5.10%, mol. mass 280 (M^+), 282 (M^+), 284 (M^+). Calculated for $C_{10}H_{16}BrClNO$: C, 42.65; H, 5.73; N, 4.98%, mol. mass 281.611. IR spectrum (ν, cm^{-1}): 1630, 1645 (C=C). The ESR spectrum was a triplet with a_N = 1.36 mT and g = 2.0056.

3-Bromo-4-vinyl-2,2,5,5-tetramethyl-Δ^3-pyrrolin-1-oxyl (XV). A mixture of 5 mmoles chloride (XIV), 5 mmoles t-BuOK, and 0.05 mmoles 18-crown-6-ether in 20 ml dry benzene was heated at reflux for 2 h. After cooling, the mixture was poured into water and extracted with ether. The extract was washed with water and aq. NaCl and dried over $MgSO_4$. The solvent was removed in vacuum to yield 1.1 g (90%) (XV) as yellow crystals with mp 84-85°C (sublimate). Found: C, 49.12; H, 5.90; N, 5.72%, mol. mass 244 (M^+), 246 (M^+). Calculated for $C_{10}H_{15}BrNO$: C, 48.99; H, 6.17; N, 5.71%, mol. mass 245.114. IR spectrum (ν, cm^{-1}): 1590, 1630 (C=C). The ESR spectrum was a triplet with a_N = 1.36 mT and g = 2.0057.

Reaction of 4-Hydroxy-2,2,6,6-tetramethyl-Δ^3-piperidin-1-oxyl (XVI) with $POCl_3$. A solution of 12.5 mmoles $POCl_3$ in 10 ml pyridine was added dropwise with stirring and ice cooling over 5 min to a solution of 0.01 mole (XVI) in 10 ml dry pyridine and the solution was maintained for 40 h at ∿20°C. The mixture was then poured into water and extracted with ether. The ethereal extract was washed with 2% HCl and aq. $NaHCO_3$, dried over $MgSO_4$, and treated with decolorizing activated charcoal. Removal of the solvent gave 0.68 g of a light red oil which was shown by gas-liquid chromatography to consist of an 85:14 mixture of olefin (XVIII) and chloride (XVII). Crystallization from pentane gave (XVII) as copper red needless with mp 110-111°C (sublimate). The mixed melting point with an authentic sample [8] was not depresed. The mother liquor was evaporated and distilled in vacuum to give (XVIII) as a light red oil which crystallizes upon standing. Recrystallization from hexane gave (XVIII) with mp 31-33°C. The IR spectrum of this compound and that of an authentic sample [8] were completely identical.

CONCLUSIONS

Synthesis are reported for a series of stable nitroxyl radicals, namely, 4-substituted 3-bromo-2,2,5,5-tetramethyl-Δ^3-pyrrolin-1-oxyls containing diazocarbonyl, chloroacetyl, iodoacetyl, acetyl, vinyl epoxide, chlorohydrin, α-chloroethyl, and α-hydroxyethyl groups at the substitutions.

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HALOGEN-CONTAINING NITROXYL RADICALS.

COMMUNICATION 5.* THE SYNTHESIS AND REACTIONS OF 2,2,5,5-TETRAMETHYL-Δ^3-PYRROLIN-1-OXYL

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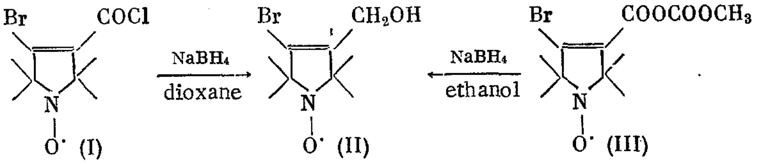
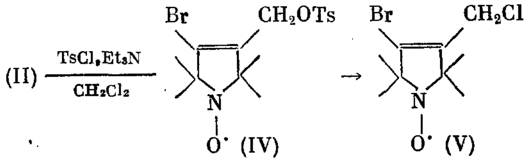
The use of spin labels and probes, synthesis of complexones, and many other applications of nitroxyl radicals have encouraged the search for convenient methods for the synthesis of simple functionally-substituted nitroxyls. 3-Bromo-4-carboxy-2,2,5,5-tetramethyl-Δ^3-pyrrolin-1-oxyl obtained by the reaction of 2,2,6,6-tetramethyl-4-oxopiperidin-1-oxyl with sodium hypobromite served as the starting material for the synthesis of a considerable number of representatives of a new series of nitroxyl radicals, namely, bromopyrrolinoxyls [1, 2].

In the present work, we extended our study of the chemical transformations of this series of nitroxyl radicals.

The reaction of $NaBH_4$ with acid chloride (I) in dioxane and with anhydride (III) in ethanol yielded alcohol (II). The treatment of anhydride (III) with $NaBH_4$ in ethanol at low temperature minimized the acylation of ethanol and gave alcohol (II) in good yield



The tosylation of alcohol (II) in CH_2Cl_2 in the presence of triethylamine leads to tosylate (IV) is about 50% yield



A byproduct is chloride (V) which is the product of the reaction of tosylate (IV) with $(C_2H_5)_3N\cdot HCl$ dissolved in CH_2Cl_2. The tosylation of alcohol (II) in benzene in the presence of $(C_2H_5)_3N$ decreases this undesired process and increases the yield of tosylate (IV) up to ∿73%. This product was reduced with $NaBH_4$ in DMSO according to Hutchins et al. [3] to yield bromopyrroline (VI) and was converted to iodide (VII) by treatment with NaI in acetone This iodide readily alkylates acetylacetone in the presence of NaH in DMF to yield diketone (VIII)

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*Communication 4, see [1].

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