1,6-Diammonium-2,4-hexadiyne Analogs of Hexamethonium

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Some new analogs of hexamethonium, based upon 1,6-diammonium-2,4-hexadiyne, in which the interquaternary distance is known with some degree of certainty, were prepared to study further the possible rigidity–activity relationships of polyalkylene diquaternary ammonium systems as ganglionic blocking agents. 1,4-Dichloro-2-butyne was used to prepare symmetrical and unsymmetrical 2,4-hexadiynes. Aminomethylation of conjugated diynes has been accomplished by Mannich reactions. Certain products exhibited marked nicotine-blocking action in guinea pig ilea.

The literature contains accounts[1,2] of the enhancement of ganglionic blocking effects, as manifested by hypotensive activity, by the introduction of an acetylenic moiety into the alkane chain of analogs and congeners of hexamethonium (1). It was suggested[2] that the triple bond forces

$$Me_3\overset{+}{N}(CH_2)_6\overset{+}{N}Me_3$$

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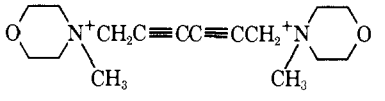
the molecule into a more extended conformation, in which the antagonist better accommodates to its *in vivo* receptor. Gill[3] has proposed that in polyalkylene bis quaternary systems, maximal ganglionic blocking activity requires a range of interquaternary distances between 6.0 and 7.8 Å. This range indicates some degree of folding of the polyalkylene chain; Dreiding models demonstrate that maximal chain extension in 1 produces an interquaternary distance of approximately 8.9 Å. Further, models of the biologically active acetylenic bis quaternary systems described in the literature[1,2] indicate that reasonable conformations are possible in which the interquaternary distances fall within the 6.0–7.8-Å range.

Biel and DiPierro[1] reported that 1,6-bis(1-morpholyl)-2,4-hexadiyne dimethiodide (2) is devoid of hypotensive activity and, since the corresponding 2-hexyne derivative 3 showed moderate activity (somewhat weaker than hexamethonium), these workers concluded that maximal extension or total rigidity of the system is detrimental to hypotensive effect. Models indicate a possible range of interquaternary distances for the bis quaternary diyne 2 of 7.8–8.4 Å, which falls at the upper limit proposed by Gill.[3] Mason and Wien[4] described the completely saturated analog of 2 and 3 as approximately 1.6 times as active a ganglionic blocker as hexamethonium. Thus, the bis(1-morpholyl) system seems an exception to the proposal that an acetylenic moiety enhances biological effects.



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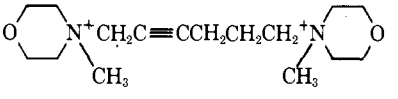

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Biel and DiPierro based their structure–activity conclusions regarding 1,6-diammonium hexadiynes on data derived from a single compound, and it seemed useful in the present work to prepare a series of α,ω-bis-quaternary hexadiynes to determine whether ganglionic inactivity is a consistent property of these fairly rigid systems. Compound 4 is a congener of hexamethonium; **5–10** were designed as varieties of combinations of large and small cationic heads (Table I).

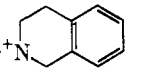
$$RCH_2C{\equiv}CC{\equiv}CCH_2R'\cdot 2Br^-$$

4, R = R′ = N^+Me_3

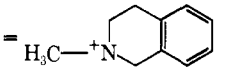
5, R = N^+Me_3; R′ = $CH_3\text{-}c\text{-}^+NC_5H_{10}$

6, R = N^+Me_3; R′ = $CH_3\text{-}c\text{-}^+N(CH_2CH_2)_2O$

7, R = R′ = $CH_3\text{-}c\text{-}^+NC_5H_{10}$

8, R = N^+Me_3; R′ = 

9, R = N^+Me_3; R′ = $CH_3\text{-}c\text{-}^+NC_4H_8$

10, R = $CH_3\text{-}c\text{-}^+NC_5H_{10}$; R′ = 

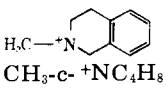
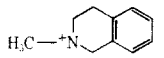
The synthetic method utilized is outlined in Scheme I and is based upon one described by Gusev, *et al.*[5,6] These workers prepared a number of α,ω-bis-quaternary ammonium 2,4-hexadiynes but they indicated no possible pharmacological considerations, and apparently the compounds were not screened for any effects. The nearly colorless, freshly distilled alcohol 13 turned wine red even at Dry Ice temperature; at room temperature it decomposed in a short time into a red-brown gel. The side product in the preparation of **13**, 2,7-dimethylocta-3,5-diyne-2,7-diol (**19**), could be recovered by extraction of the pot residue from distillation of **13**. This stable, crystalline diol could be pyrolyzed in the presence of potassium carbonate to afford moderate additional amounts of **13**.

Mannich reactions on **13** failed; however, the acetate ester **14** underwent normal condensations with paraformaldehyde and a variety of secondary amines. These results are consistent with findings of earlier workers[7] with respect to attempted Mannich condensations on α-hydroxyacetylenes. The Mannich product of **14** with piperidine could not be obtained analytically pure; however, the free alcohol derivative **16** (NRR′ = 1-piperidyl) gave a correct analysis. The pyrolysis reaction (**16** → **17**) could be controlled only with 10-g quantities or less; with larger amounts, control of heat transfer was difficult and the pot contents turned into an amorphous black solid. The second Mannich step (**17** → **18**) proceeded normally and with minimal difficulty.

Several of the 1,6-diamino-2,4-hexadiynes (**18**) did not yield satisfactory elemental analyses; spectral (ir and nmr) data were consistent with the proposed structures and tlc analysis indicated homogeneity. The diamines were converted to their bis quaternary salts with methyl bromide, and these gave satisfactory elemental analyses. Gusev, *et al.*,[6] indicated similar difficulties with α,ω-diamino-2,4-hexadiynes. The salts **4–10** were stable at ambient temperature and were not hygroscopic. All of the ana-

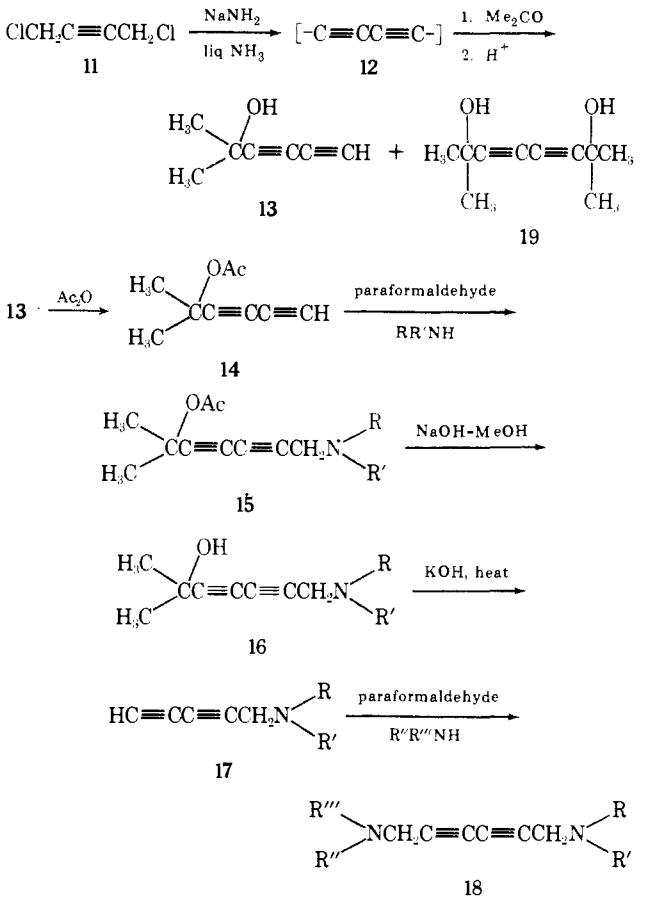
Table I. 1,6-Diammonium-2,4-hexadiynes

$RCH_2C{\equiv}CC{\equiv}CCH_2R' \cdot 2Br^-$

Compd no.	R	R′	Mp, °C	Yield, %	Formula	Analyses
4	Me_3N^+	Me_3N^+	200–230[a] dec	55	$C_{12}H_{22}Br_2N_2$	C, H, N
5[b]	Me_3N^+	CH_3-c-$^+NC_5H_{10}$	185–215[a] dec	99	$C_{15}H_{26}Br_2N_2$	C, H, Br, N
6	Me_3N^+	CH_3-c-$^+N(CH_2CH_2)_2O$	190–220[a]	99	$C_{14}H_{24}Br_2N_2O$	C, H, Br, N
7	c-$C_5H_{10}N^+$-CH_3	CH_3-c-$^+NC_5H_{10}$	200–230[c] dec	77	$C_{18}H_{30}Br_2N_2$	C, H, N
8	Me_3N^+		175–190[d] dec	41	$C_{19}H_{26}Br_2N_2$	C, H, N
9	Me_3N^+	CH_3-c-$^+NC_4H_8$	200–220[e]	66	$C_{14}H_{24}Br_2N_2$	C, H, N
10	c-$C_5H_{10}N^+$-CH_3		160–190[f] dec	33	$C_{22}H_{30}Br_2N_2$	C, H, N
2[g]	c-$O(CH_2CH_2)_2N^+$-CH_3	CH_3-c-$^+N(CH_2CH_2)_2O$	190–220[a]	36	$C_{16}H_{26}Br_2N_2O_2$	C, H, Br, N

[a] From absolute methanol. [b] Gusev, *et al.*,[6] prepared the iodide salt of this compound. [c] From 2-propanol–ether. [d] From 2-propanol–ethanol. [e] From absolute ethanol. [f] From 2-propanol. [g] Prepared from 1,6-bis(dimethylamino)-2,4-hexadiyne (Aldrich Chemical Co.). Biel and DiPierro[1] reported the iodide salt of this compound.

Scheme I. Preparation of 1,6-Diamino-2,4-hexadiynes



lytically pure diquaternary salts demonstrated very broad (20–30°) decomposition ranges. Gusev, *et al.*,[6] did not report melting point data for hexadiyne bis quaternary iodides. In contrast, Biel and DiPierro[1] reported a 1° melting range for the diiodide salt of **2**. Driedger and Isaacson[8] recently noted that 2,4-hexadiyne-1,6-bis(chloroformate) and 1,6-dichloro-2,4-hexadiyne tend to decompose violently from mechanical shock or when stored under reduced pressure. In view of the similarity between these compounds and **4**–**10**, the broad decomposition ranges for the latter are not surprising, nor is the gradual decomposition over a wide temperature range noted in differential thermal analysis of **4**.

The absence of absorption bands in the 2000–1950- and 850-cm^{-1} regions of the infrared spectra of the bis quaternary diynes confirmed the absence of an allene system[9-11] in all of the products. Nmr spectra of the bis quaternary products and of all pertinent intermediates were consistent with the proposed 2,4-hexadiyne structures.

Table II. Nicotine-Blocking Effects of Bis Quaternary Hexadiynes

Compd no.	ED_{50} (in μg/ml) *vs.* nicotine
2	100
4	90
5	10
6	8
7	100
8	35
9	1.0
10	*a*
Hexamethonium	1.0

[a] Antagonizes acetylcholine.

Pharmacology. Guinea pig ilea (three ilea per compound) were superfused with Tyrode's solution to which various concentrations of the compound being studied were added. Dose-response curves to acetylcholine (ACh) (0.001, 0.002, 0.004, and 0.008 γ) and to nicotine (2, 4, and 8 γ) were used as controls while the ileum was superfused with Tyrode's solution. The drug was then added to the solution and the doses of ACh and nicotine were repeated and compared to the control. The ileum was then returned to regular Tyrode's superfusion to confirm that the test compound could be washed out. Those compounds which showed some effectiveness in blocking nicotine were washed out by Tyrode's solution within 10 min. See Table II. Compound **10** at 50 γ/ml showed 50% block of ACh after 1–2 min and complete block of nicotine after 5–7 min of superfusion. None of the other compounds blocked ACh at the dose levels employed (up to 100 γ/ml).

Discussion

While certain of the compounds demonstrated considerable nicotine-blocking activity, none was more potent than hexamethonium, and only one, **9**, was equipotent. Based on these data, it is concluded that the added rigidity and enforced chain extension in the hexadiyne system do not enhance biological activity, although these parameters are not necessarily detrimental to nicotine-blocking effects (compound **9**). It may be significant that the closest possible interquaternary distance in these systems (7.8 Å) coincides with the upper limit proposed by Gill[3] for

maximal ganglionic blocking activity. It seems noteworthy that the three most potent compounds, **5**, **6**, and **9**, each bear a trimethylammonium head and a cyclic ammonium head and that like ammonium groups in the same molecule confer low activity in this series (**2**, **4**, and **7**). Further, the order of potency in the more active members of the series (**9** > **6** ~ **5**) parallels the steric compactness of the cyclic amines involved (pyrrolidine > morpholine ~ piperidine). This is indicative that in compound **9**, the trimethylammonium and pyrrolidinium groups adopt a syn orientation at the receptor, giving an interquaternary distance of 7.8 Å. The low activity of the bis-cyclic ammonium compounds **2** and **7** suggests that a trimethylammonium substituent possesses the highest intrinsic activity. The work reported herein can be interpreted to support the Gill hypothesis for optimal interquaternary distance in the bis quaternary systems.

Experimental Section

Boiling points are uncorrected. Melting points were determined in open glass capillaries using a Thomas-Hoover Uni-Melt apparatus and are corrected. Infrared spectra were obtained on a Beckman IR-10 instrument. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn., and by the Microanalytical Service, College of Pharmacy, The University of Iowa. Where analyses are indicated by symbols of the elements, the analytical results were within ±0.4% of the theoretical values.

2-Methylhexa-3,5-diyn-2-ol (13). This was prepared by the method of Armitage, *et al.*,[12] using 49.2 g (0.4 mol) of 1,4-dichloro-2-butyne (Aldrich Chemical Co.): yield, 22.9 g (53%); bp 38–40° (0.8 mm) [lit.[12] bp 39.5° (0.5 mm)].

2-Methyl-2-acetoxyhexa-3,5-diyne (14). This was prepared by the method of Gusev and Kucherov[5] from 11.0 g (0.102 mol) of **13**, 16.3 g (0.16 mol) of acetic anhydride, and 10 drops of 85% H_3PO_4: bp 30–32° (0.5 mm) [lit.[5] bp 50–52° (0.7 mm)]; yield, 8.85 g (73%).

1-Dimethylamino-6-methyl-6-acetoxyhepta-2,4-diyne (20). This was prepared by the method of Gusev, *et al.*,[6] using 40.5 g (0.27 mol) of **14**, 12.15 g (0.40 mol) of paraformaldehyde, 24.3 g (0.54 mol) of dimethylamine, 0.5 g of cupric acetate, and 400 ml of dioxane: bp 92–98° (0.25 mm) [lit.[6] bp 96–97° (0.2 mm)]; yield, 40.35 g (72%) of a yellow oil.

1-Dimethylamino-6-methylhepta-2,4-diyn-6-ol (21). Compound **20** (32.0 g, 0.15 mol), 9.27 g (0.23 mol) of NaOH, and 500 ml of anhydrous methanol were stirred and heated at 70° for 18 hr. Water (50 ml) was added and the resulting mixture was concentrated under reduced pressure. The residue was extracted with ether and this ether solution was extracted with 100 ml of 5 *N* HCl in three portions. The combined acid extract was treated with excess NH_4OH and the solid which separated was collected on a filter and recrystallized from *n*-hexane in a Soxhlet apparatus to yield 19.8 g (78%) of white needles, mp 104.5–106° (lit.[6] mp 105.5–106°).

1-Dimethylaminopenta-2,4-diyne (22). Compound **21** (4.4 g, 0.027 mol) was heated to its melting point in the presence of one pellet of KOH under 15–20 mm of pressure and then was maintained at 115° for 0.25 hr. The reaction mixture was dissolved in $CHCl_3$ and filtered, and $CHCl_3$ was removed from the filtrate under reduced pressure at room temperature. Distillation of the resulting brown slurry gave 0.84 g (79% based upon the amount of starting material recovered) of a light yellow oil, bp 26° (0.5 mm) [lit.[6] bp 43–44° (7 mm)]. The solid pot residue was recrystallized from *n*-hexane to give 2.74 g (67%) of starting material **21**.

1,6-Bis(dimethylaminohexa-2,4-diyne) (23). This was prepared by a modification of a method of Gusev, *et al.*[6] Compound **22** (3.2 g, 0.03 mol), 2.0 g (0.045 mol) of dimethylamine, 1.8 g (0.06 mol) of paraformaldehyde, 0.1 g of cupric acetate, and 15 ml of dioxane were refluxed with stirring for 2 hr. The cooled reaction mixture was treated with 5 ml of water. The resulting mixture was extracted with 200 ml of ether in three portions; the combined ethereal extract was extracted with 75 ml of 5 *N* HCl in three portions. The acid extract was treated with excess NH_4OH and the resulting mixture was extracted with ether. This extract was dried ($MgSO_4$) and the ether was removed under reduced pressure. The brown residue was distilled at 97.5–98° (2.5 mm) to give 3.25 g (66%) of a light yellow liquid which solidified on standing to give very low melting crystals, mp 32–33° [lit.[6] bp 75° (0.8 mm)].

1-Dimethylamino-6-(1-piperidyl)hexa-2,4-diyne (24). This was prepared by the method described for **23** using 1.35 g (0.0126 mol) of **22**, 1.62 g (0.019 mol) of piperidine, 0.75 g (0.025 mol) of paraformaldehyde, 0.2 g of cupric acetate, and 75 ml of dioxane. The brown crude product was distilled at 96–97° (0.1 mm) to give 1.42 g (55%) of product [lit.[6] bp 110–111° (1 mm)].

1-Dimethylamino-6-(4-morpholyl)hexa-2,4-diyne (25). This was prepared by the method described for **23** using 1.0 g (0.0093 mol) of **22**, 1.22 g (0.014 mol) of morpholine, 0.56 g (0.0186 mol) of paraformaldehyde, 0.2 g of cupric acetate, and 75 ml of dioxane. The brown crude product was distilled at 102–103° (0.05 mm) to yield 0.9 g (47%) of product [lit.[6] bp 119° (0.85 mm)].

1-(1-Piperidyl)-6-methyl-6-acetoxyhepta-2,4-diyne (26). Compound **14** (15 g, 0.10 mol), 6.0 g (0.2 mol) of paraformaldehyde, 12.75 g (0.15 mol) of piperidine, 0.5 g of cupric acetate, and 100 ml of dioxane were treated as described for preparation of **20**: yield, 17.7 g (72%); bp 118–125° (0.075 mm); ir (film) 1745 cm^{-1} (C=O).

1-(1-Piperidyl)-6-methylhepta-2,4-diyn-6-ol (27). Compound **26** (8.3 g, 0.034 mol) was treated with 1.92 g (0.048 mol) of NaOH in 250 ml of anhydrous methanol as described for **21**. The tan crude product was recrystallized from *n*-hexane to afford 2.29 g (33%) of white crystals: mp 52–54°; ir ($CHCl_3$) 3050 cm^{-1} (OH). *Anal.* ($C_{13}H_{19}NO$) C, H, N.

1-[2-(1,2,3,4-Tetrahydroisoquinolyl)]-6-methyl-6-acetoxy-2,4-heptadiyne (28). Compound **14** (18 g, 0.12 mol), 7.2 g (0.24 mol) of paraformaldehyde, 24.0 g (0.18 mol) of 1,2,3,4-tetrahydroisoquinoline, 0.5 g of cupric acetate, and 150 ml of dioxane were heated at 80–85° with stirring for 4 hr. Water (10 ml) was added to the cooled reaction mixture and this mixture was extracted with ether. The ether extract was extracted with 100 ml of 5 *N* HCl in three portions. This acidic fraction was treated with excess NH_4OH and the resulting mixture was extracted with ether. The ethereal extract was dried ($MgSO_4$) and filtered, and ether was removed from the filtrate under reduced pressure. The liquid residue was treated with 20 ml of ethanol and this mixture was stored in the cold for 78 hr. The solid which separated was collected on a filter, washed with cold ethanol, and dried under reduced pressure at room temperature to yield 19.22 g (54%) of light tan crystals: mp 70–74°; ir (KBr) 1740 cm^{-1} (C=O). *Anal.* ($C_{19}H_{21}NO_2$) C, H, N.

1-[2-(1,2,3,4-Tetrahydroisoquinolyl)]-6-methyl-2,4-heptadiyn-6-ol (29). Compound **28** (5.8 g, 0.0197 mol) and 1.2 g (0.03 mol) of NaOH in 150 ml of methanol were heated at 70° with stirring for 18 hr. The oil obtained by the extraction procedure described for **21** was taken up in ethanol and a solid was precipitated by the addition of ice. This was recrystallized from *n*-hexane to give 2.37 g (48%) of a light tan solid which was recrystallized from Skellysolve B to give a white product: mp 60–65°; ir (KBr) 3150 cm^{-1} (OH). *Anal.* ($C_{17}H_{19}NO$) C, H, N.

1-(1-Piperidyl)-2,4-pentadiyne (30). Compound **27** (2.06 g, 0.01 mol) was fused in the presence of one pellet of KOH under 20 mm of pressure, and the temperature was maintained at 65° for 1 hr. The reaction mixture was dissolved in $CHCl_3$ and filtered, and the product was isolated from the filtrate by dry column chromatography (neutral alumina, $CHCl_3$) to give 0.65 g (48%) of a yellow liquid: ir (film) 3300 cm^{-1} (C≡CH).

A methyl bromide salt was prepared from 0.05 g (0.00035 mol) of **30** and 17.3 g (0.182 mol) of methyl bromide in 8 ml of 1-butanol in a sealed Carius tube at room temperature. After 14 days, the tan precipitate was recrystallized from 2-propanol–hexane to give 0.008 g (10%) of product, mp 145–155° dec. *Anal.* ($C_{11}H_{16}BrN$) C, H, N.

1-[2-(1,2,3,4-Tetrahydroisoquinolyl)]-2,4-pentadiyne (31). This was prepared from 2.30 g (0.009 mol) of **29** as described for **30**: yield, 0.36 g (20%) of a yellow liquid; ir (film) 3300 cm^{-1} (C≡CH).

A methyl bromide salt was prepared from 0.15 g (0.00077 mol) of **31**, 17.3 g (0.182 mol) of methyl bromide, and 10 ml of 2-propanol as described for **30**. The tan precipitate was recrystallized from 2-propanol–hexane to give 0.024 g (11%) of a tan solid, mp 160–169°. *Anal.* ($C_{15}H_{16}BrN$) C, H, N.

1,6-Bis(1-piperidyl)-2,4-hexadiyne (32). Paraformaldehyde (0.41 g, 0.014 mol) and 0.87 g (0.01 mol) of piperidine in 150 ml of dioxane were heated and stirred at 70° for 1.5 hr. A hot solution of 0.2 g of cupric acetate in 20 ml of dioxane was then added, followed by 0.56 g (0.0038 mol) of **30** in 20 ml of hot dioxane. This combined mixture was stirred and heated at 70° for 18 hr, then 50 ml of water was added, and the resulting mixture was extracted with ether. The ethereal extract was extracted with 90 ml of 5 *N*

HCl in three portions, the acidic extract was basified with NH_4OH, and the resulting mixture was extracted with ether. Ether was removed from this extract under reduced pressure and the solid residue was recrystallized from petroleum ether (bp 37.6–51.2°) to give 0.55 g (59%) of **32**, mp 58–59°. *Anal.* ($C_{16}H_{24}N_2$) C, H, N.

1-[2-(1,2,3,4-Tetrahydroisoquinolyl)]-6-(1-piperidyl)-2,4-hexadiyne (33). This was prepared by the method described for **32**, utilizing 0.078 g (0.0026 mol) of paraformaldehyde, 0.16 g (0.00019 mol) of piperidine, 0.1 g of cupric acetate, and 0.25 g (0.0013 mol) of **31**. The combined reaction mixture was stirred and heated at 70° for 10 hr. Water (25 ml) was added and the resulting mixture was extracted as described for **32** to give an oil which was subjected to dry column chromatographic treatment (neutral alumina, $CHCl_3$) to provide 0.131 g (35%) of a light tan oil.

1-[2-(1,2,3,4-Tetrahydroisoquinolyl)]-6-dimethylamino-2,4-hexadiyne (34). This was prepared by the method described for **32**, utilizing 0.48 g (0.016 mol) of paraformaldehyde, 1.33 g (0.012 mol) of 1,2,3,4-tetrahydroisoquinoline, 0.2 g of cupric acetate, 0.88 g (0.0082 mol) of **22**, and 155 ml of dioxane. The combined reaction mixture was heated at 75° and stirred for 16 hr. Water (25 ml) was added and the resulting mixture was extracted as described for **32** to give a brown oil which was subjected to dry column chromatographic separation (neutral alumina, $CHCl_3$) to give 1.08 g (52%) of a straw-colored oil.

1-Dimethylamino-6-(1-pyrrolidyl)-2,4-hexadiyne (35). This was prepared by the method described for **32**, utilizing 0.88 g (0.0124 mol) of pyrrolidine, 0.495 g (0.0165 mol) of paraformaldehyde, 0.2 g of cupric acetate, 0.88 g (0.0082 mol) of **22**, and 90 ml of dioxane. This combined reaction mixture was stirred and heated at 75° for 16 hr. The product was isolated as described for **33** to give 0.60 g (38%) of a brown oil.

Bis Quaternary Ammonium Compounds. A sealed Carius tube containing the appropriate 1,6-diamino-2,4-hexadiyne and a tenfold molar excess of methyl bromide in 2-propanol was permitted to stand at room temperature for 48 hr. The resulting white precipitate was collected on a filter and recrystallized. See Table I.

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Notes

Use of Sodium Cyanoborohydride in the Preparation of Biologically Active Nitroxides

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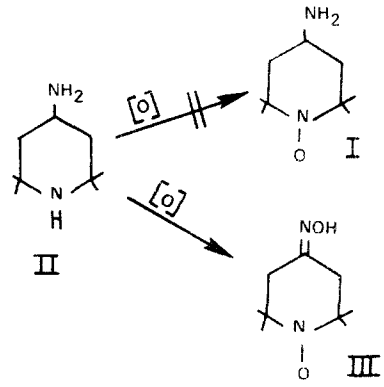
In recent years, the use of nitroxides as free-radical probes in the study of biologically significant reactions has come of age.[1-7] Unfortunately, synthetic limitations have hindered the development of many free-radical analogs of important therapeutic agents. Such is the case with 4-amino-2,2,6,6-tetramethylpiperidinooxyl (I), an intermediate in the preparation of medicinally active compounds. Rosantsev and Kokhanov[8] have found that all attempts at direct catalytic oxidation of 4-amino-2,2,6,6-tetramethylpiperidine (II) to the corresponding free radical I led to the isolation of an oxime radical III, which could not be reduced to I. The authors[8] were finally able to obtain the desired free radical I after a laborious synthetic sequence involving a reduction and oxidation. Reaction of 2,2,6,6-tetramethyl-4-piperidone (IV) with hydroxylamine gave the corresponding oxime V. Reduction using sodium in *n*-pentyl alcohol gave 4-amino-2,2,6,6-tetramethylpiperidine (VI). Subjecting the piperidine VI to acetic anhydride gave the corresponding 4-acetamido-2,2,6,6-tetramethylpiperidine (VII). Oxidation of VII with hydrogen peroxide



followed by hydrolysis gave the desired free radical I.

Recently, Borch, *et al.*,[9,10] have discovered the selective reductive powers of sodium cyanoborohydride. They observed that ketoximes could be reduced to the corresponding *N*-alkylhydroxylamines without overreduction to the amines. Furthermore, under mild conditions, *e.g.*, pH 6–8 and at ambient temperature, aldehydes and ketones can be reductively aminated to the corresponding primary, secondary, and tertiary amine without direct reduction of the aldehyde or ketone. When the pH is lowered to 3–4, the reduction of aldehydes or ketones is sufficiently rapid so as to make this reaction synthetically useful. With this in mind, we felt that these conditions might be mild enough to allow a reductive amination of a ketone possessing a nitroxide without eliminating the free radical. For example, the reaction of 4-oxo-2,2,6,6-tetramethylpi-

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