Preparation and Properties of a Structually Novel Heterocyclic Dispiro Compound, 3,10-Dimethyl-3,10-diazadispiro[5.0.5.4]hexadeca-1,4,8,11-tetraene

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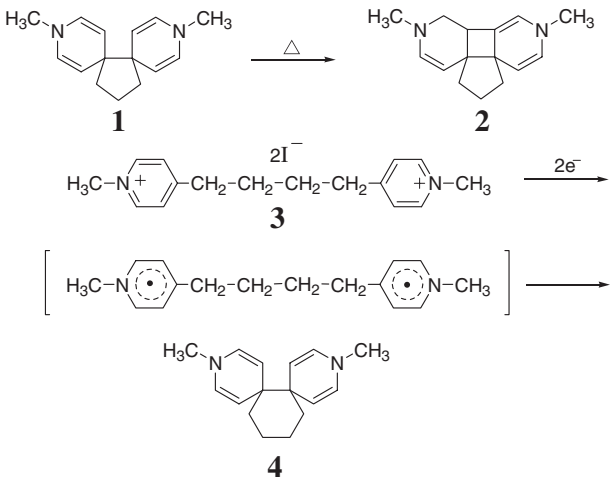
The two-electron reduction of **3** with sodium amalgam in degassed acetonitrile affords **4** in quantitative yield. Under deoxygenerated conditions, **4** is stable for a long time at room temperature, but slowly undergoes an opening of the cyclohexane ring skeleton with elimination of methyl groups to yield **5** at about 200 °C. At the same time, a small amount of **6** is obtained by fission of a CC single bond of the cyclohexane ring skeleton with the transfer of hydrogen atom.

Heterocyclic spiro compounds have so far been found in nature, and certain aza-spiro compounds are used in medicine as angiogenesis inhibitors.[1–4] In the course of our studies directed towards elucidating physicochemical properties of pyridinyl diradicals, we have prepared 3,10-dimethyl-3,10-diazadispiro-[5.0.5.3]pentadeca-1,4,8,11-tetraene (**1**), a novel dispiro compound characterized by a cyclopentane ring with vicinal spirocyclic dihydropyridine groups.[5] Of interest is the experimental fact that **1** exhibits peculiar behavior in thermal reaction. Upon heating at 160 °C, an intramolecular cyclization reaction takes place with the transfer of hydrogen atom to give 8,13-diaza-8,13-dimethyltetracyclo[9.4.0.0^{1,5}.0^{5,10}]pentadeca-6,9,14-triene (**2**). At higher temperatures above 160 °C, **1** undergoes mostly a decomposition reaction to give 1,3-bis(*N*-methyl-1,4-dihydropyridinylidene)propane and 4,4′-(1,3-propanediyl)bis(*N*-methyl-1,4-dihydropyridine) as the intermediates and, subsequently, their isomerization reactions take place respectively to give **2**. To carry out systematic study on the chemistry of dispiro compounds,[6] it is essential to prepare higher homologues of **1**. With this background, we prepare a structurally novel dispiro compound, 3,10-dimethyl-3,10-diazadispiro[5.0.5.4]hexadeca-1,4,8,11-tetraene (**4**) by two-electron reduction of 1-methyl-4-[4-(1-methyl-4-pyridinio)butyl]pyridinium diiodide (**3**) and present its thermal behavior.



Reduction of **3** was carried out with sodium amalgam in degassed acetonitrile.[7] The reduction process was followed by UV–vis absorption spectroscopy. Figure 1 shows the spectral change during the course of reduction, where the spectral line (a) corresponds to the spectrum of **3**. After 2 h of reduction, the absorption maximum at about 330 nm was decreased in intensity and the spectrum changed into the spectral line (b) with a long absorption tail. After 7 h of reduction, the spectrum changed into the spectral line (d), which resembles the absorption spectrum of **1**. At this stage, no spectral change was observed upon further reduction. Note that no EPR signals due to free radicals were observed at all during the reduction process. This suggests that **3** undergoes a relatively fast two-electron reduction to give a product.

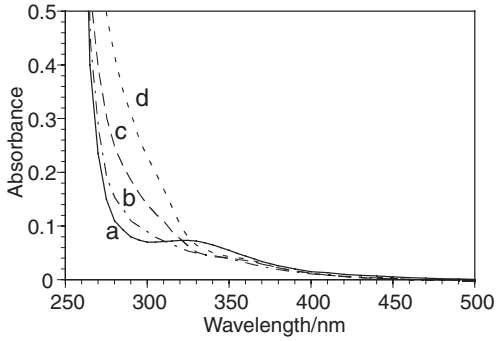


Figure 1. Absorption spectral change during the course of reduction of **3** (1.0×10^{-2} mmol) with 3% sodium amalgam (2.2×10^{-2} mmol) in degassed acetonitrile (5 mL) at 0 °C: (a) before reduction, (b) after 2 h, (c) after 4 h, and (d) after 7 h.

Since the reduction product is unstable in the presence of oxygen,[8] the characterization was carried out in a sealed tube under vacuum. In Figure 2 is shown the ^{1}H NMR spectrum of the reduction product.[9] The NMR spectrum suggests that the product should have a symmetric structure because the spectral features are very simple. Analyses show that a clear correlation exists between the proton assignments obtained by means of the spin-decoupling and H,C-COSY techniques, indicating the formation of a single component as the final reduction product. By reference to the ^{1}H NMR spectra of 1,2-bis(*N*-methyl-4-pyridyl)ethylene and **1**,[5,10] the structural assignment can be made reasonably such that the product should possess the structure of 3,10-dimethyl-3,10-diazadispiro[5.0.5.4]hexadeca-1,4,8,11-tetraene (**4**). A careful analysis of the ^{13}C NMR spectrum lends further support for the above structural assignment.[5] Consequently, **4** is characterized by a cyclohexane ring skeleton with

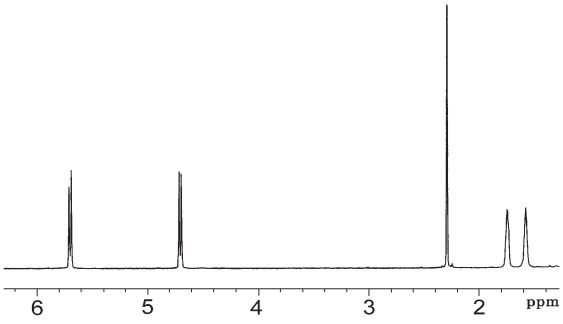
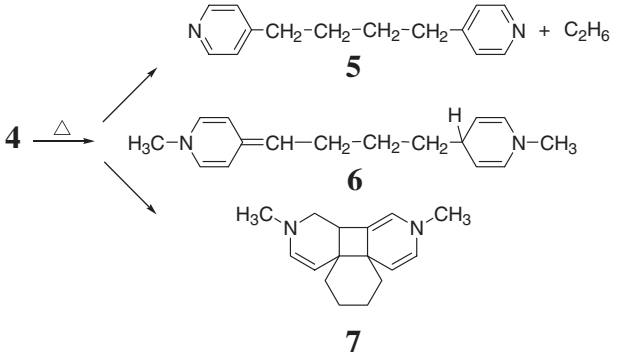


Figure 2. 400 MHz ^{1}H NMR spectrum of **4** in C_6D_6.

vicinal spirocyclic dihydropyridine rings. In this connection, it is noted that Suzuki et al. have recently prepared a hexabenzo derivative of **4**.[11]

Reduction product **4** is stable to light for long time in degassed conditions. That is, no photochemical reaction takes place when **4** is irradiated by light with longer wavelengths than 310 nm. Further, no thermal decomposition reaction is observed upon continued heating of **4** for 20 h at 150 °C. In contrast, the decomposition reaction takes place slowly at higher temperatures above 200 °C to yield 4-[4-(4-pyridyl)butyl]pyridine (**5**) as the main product.[12,13] The formation of **5** can be readily accounted for in terms of a ring-opening reaction of the cyclohexane moiety with the concomitant elimination of methyl groups.[14,15] Competitively, the thermal reaction also gives rise to a small amount of 1-methyl-4-[4-(1-methyl-4-(1,4-dihydro-4-pyridyl)butylidene]-1,4-dihydropyridine (**6**)[16] by fission of a CC single bond of the cyclohexane ring with the transfer of hydrogen atom. Integration of the characteristic ^{1}H NMR signals reveals that the product ratio of **5** and **6** is about 5:1. At the same time, an isomerization reaction takes place by intramolecular cyclization with the transfer of hydrogen atom to give a trace amount of 9,14-diaza-9,14-dimethyltetracyclo[10.4.0.0^{1,6}.0^{6,11}]-hexadeca-7,10,15-triene (**7**).[17] In short, **4** is shown to undergo thermally the demethylation reaction in preference to the isomerization reactions. It can thus be pointed out that this is a marked difference in thermal reactivity between **1** and **4**. The thermal reaction products of **4** are given below. Further study on **4** is now in progress and details will be discussed elsewhere in the near future.



References and Notes

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7 Diiodide **3** was synthesized by reaction of methyl iodide with 4-[4-(4-pyridyl)butyl]pyridine prepared by employing procedures given by Richard et al. See: D. H. Richard, N. F. Scilly, and F. J. Williams, *Chem. Ind.*, **1970**, 1298. **3**; 400 MHz ^{1}H NMR (DSMO-d_6) δ 8.84 (d, $J = 6.4$ Hz, 4H), 7.98 (d, $J = 6.4$ Hz, 4H), 4.26 (s, 6H), 2.91 (br.s, 4H), 1.67 (br.s, 4H).

8 The reduction product also exhibits a high reactivity to air oxygen as **1** does and, hence, undergoes an oxidative decomposition reaction to yield *N*-methyl-4-pyridone and other oxidative products. This seems to be a common property inherent to a series of these dispiro compounds, which can be ascribed to the existence of dihydropyridine groups responsible for a high reducing power.[5]

9 **4**; 400 MHz ^{1}H NMR (C_6D_6) δ 1.56–1.61 (4H, m), 1.72–1.79 (m, 4H), 2.30 (s, 6H), 4.71 (d, $J = 7.81$ Hz, 4H), 5.70 (d, $J = 7.81$ Hz, 4H); ^{13}C NMR (C_6D_6) δ 19.9 (CH_2), 37.4 (CH_2), 39.7 (CH_3), 42.5 (C), 103.7 (CH), 130.2 (CH).

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12 **5**; 400 MHz ^{1}H NMR (C_6D_6) δ 8.54 (d, $J = 5.4$ Hz, 4H), 6.59 (d, $J = 5.4$ Hz, 4H), 2.07 (br.s, 4H), 1.16 (br.s, 4H).

13 Formation of ethane is confirmed by the proton signal at 0.58 ppm.

14 The opening of cyclohexane ring is supported by preliminary AM1 calculations that **4** has a relatively long CC single bond of ca. 1.57 Å at the position joining directly two dihydropyridine rings. This aspect in bonding will be reasonably interpreted in terms of a through-bond interaction.[15]

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16 **6**; 400 MHz ^{1}H NMR (C_6D_6) δ 5.77 (d, $J = 7.8$ Hz, 1H), 5.72 (d, $J = 6.8$ Hz, 1H), 5.53 (d, $J = 7.8$ Hz, 2H), 5.31 (d, $J = 7.8$ Hz, 1H), 4.95 (d, $J = 6.8$ Hz, 1H), 4.78 (t, $J = 8.0$ Hz, 1H), 4.41 (dd, $J = 7.8$ Hz, 3.4 Hz, 2H), 3.17 (m, 1H), 2.25 (s, 3H), 2.11 (s, 3H), 2.10–2.30 (m, 2H), 1.20–1.40 (m, 4H).

17 The identification of **7** was made tentatively by reference to the NMR spectrum of **2**. Further, the proton signals observed at 5.75 ppm as a singlet, at 5.69 ppm as a doublet ($J = 6.8$ Hz), and at 4.68 ppm as a doublet ($J = 6.8$ Hz) suggest the existence of a 3,4,4-trisubstituted *N*-methyl-1,4-dihydropyridine structure in **7**. It seems however that further study may need to be done on this assignment in the future.

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