NOVEL SYNTHESIS AND PROPERTIES OF [n](2,4)PYRIDINOPHANES AND [n](2,4)QUINOLINOPHANES

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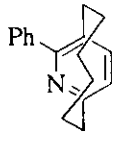
Abstract– A new short synthesis of cyclohexenone-annulated [n](2,4)pyridinophanes (n=9-7), which were easily converted to [n](2,4)quinolinophanes (n=9-7), respectively, was accomplished by the reaction of 3-amino-2-cyclohexenone with 2-cycloalkenones.

The remarkable chemical and physical properties of strained cyclophanes[1-4] and heterophanes[1] continue to fascinate many chemists. In the field of heterocyclic [n]paracyclophanes,[5,6] the smallest known compound is [6](2,5)pyridinophane (**1**).[5] The smallest known metapyridinophanes so far obtained are 3-halogeno-substituted [6](2,4)pyridinophanes,[7] [6](2,6)pyridinophane,[8] [7](3,5)pyridinophane,[9] 3-chloro[6](2,4)quinolinophane (**2**), and [8](2,4)quinolinophane (**16b**).[10,11] Previously, we have studied the preparation and static and dynamic behavior of [n](2,4)pyridinophanes (n=9-6), (**3**)[12] and azuleno-annulated [n](2,4)pyridinophanes (**4**) (n=9-6) (Figure 1).[13] The synthetic reaction consists of an enamine-alkylation process of (vinylimino)phosphorane[14] and 2-aminoazulene with 2-cycloalkenones, respectively, subsequent condensation of the nitrogen moiety with the carbonyl function, and dehydrogenation with 10% Pd/C or DDQ. Just in the case of 2-aminoazulene, a Michael-type addition of β-amino enones to α,β-unsaturated ketones and subsequent condensation gave dihydropyridines.[15] Thus, we applied the reaction to provide a new simple methodology for constructing a series of cyclohexenone-annulated [n](2,4)pyridinophanes (**10a-c**), which were conveniently converted to a series of [n](2,4)quinolinophanes (**16a-c**) (n=9-7) including the known [8](2,4)quinolinophane (**16b**). The static and dynamic properties of the [n](2,4)pyridinophanes and [n](2,4)quinolinophanes were studied as well.

The thermal reactions of 3-amino-2-cyclohexenone (**5**) (1 mmol) with 2-cycloalkenones (**6a-c**) (n=9-7) (2 mmol) in toluene (2 mL) in the presence of 4 Å molecular sieves (100 mg) and a catalytic amount of a dehydrogenating agent (10% Pd/C) under reflux for 96 h afforded [n](2,4)pyridinophanes (**10a**) (71%),



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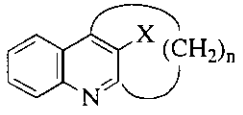
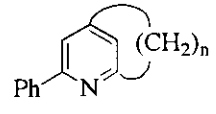
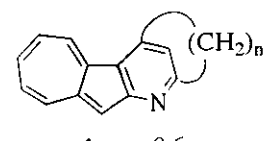


2 : X = Cl; n = 6
16b : X = H; n = 8



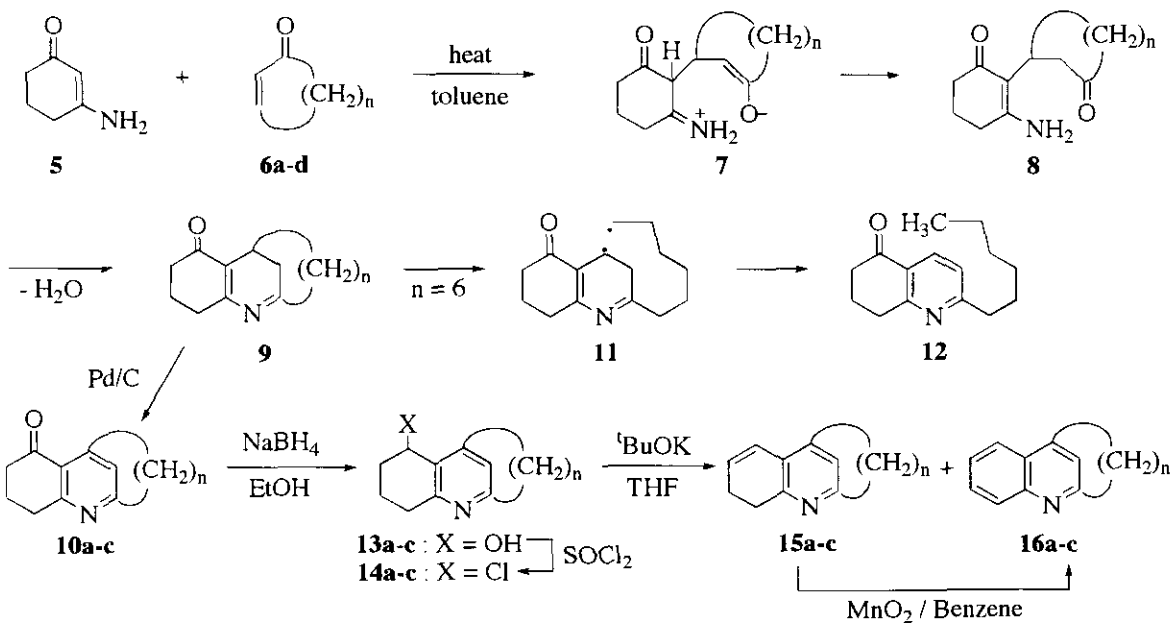
3 : n = 9-6



4 : n = 9-6

Figure 1

(**10b**) (60%), and (**10c**) (46%), respectively (Scheme 1 and Table 1).[16] However, the reaction of **5** with **6d** (n=6) in a similar fashion resulted in the formation of pyridine (**12**) (7%).[16,17] The postulated reaction pathways for the formation of **10a-c** and **12** are also shown in Scheme 1. Enamine alkylation of **5** to the β-carbon atom of **6a-d** gives **7**, and subsequent hydrogen migration regenerate the β-amino enone moiety in **8**. The intermediate (**8**) undergoes an intramolecular condensation to give dihydropyridine (**9**), and the following aromatization with 10% Pd/C results in the formation of [n](2,4)pyridinophanes (**10a-c**). In the case of the constrained (**9**) (n=6), allylic bond cleavage probably occurs to afford **11**, which undergoes aromatization to give **12**, albeit in low yield. The intermediate (**9**) (n=6), which has a hexamethylene bridge, seems to be resistant to the dehydrogenation in the presence of 10% Pd/C, suggesting a high degree of ring strain. Reduction of pyridinophanes (**10a-c**) with $NaBH_4$ produced alcohol derivatives (**13a-c**)[16] in 99% yield. On treatment with $SOCl_2$, compounds (**13a-c**) were converted to chlorides (**14a-c**)[16] in 86, 68, and 93% yields, respectively. The dehydrochlorination of **14a-c** with *t*-BuOK in THF afforded mixtures of [n](2,4)quinolinophanes (**16a-c**) and their dihydrogenated derivatives (**15a-c**), respectively, and the mixtures were aromatized with activated MnO_2 in benzene to give pure [n](2,4)quinolinophanes (**16a-c**) (Table 1)[16] in 44, 61, and 52% yields, respectively.



Scheme 1 **a** : n=9; **b** : n=8; **c** : n=7; **d** : n=6

Compound (**16b**) is known and the structure was assigned on the basis of comparison of the physical data with those reported in the literature.[10,11] All the ^1H NMR spectra (Table 1) (see the convenient numbering of the methylene in Figure 2) of **10a-c** as well as **16a-c** correlated well with each other and are in good accordance with the proposed structures. A characteristic feature of these compounds is the equivalence of the geminal hydrogens at the "benzylic" positions, H-1' and H-n'. These protons appear as

two triplets, a triplet and a broad singlet, a doublet of doublet and a triplet, and two doublets of doublets (Table 1). This splitting pattern is indicative of a rapid flipping of the methylene chain of **10a-c** and **16a-c**. Generally, the four "benzylic" protons of [6](2,4)pyridinophanes exhibit different chemical shifts, suggesting that the bridge flipping of the hexamethylene chain is slow at room temperature.[12,13] The ^{1}H NMR spectra of **10c** were recorded at various temperatures. At 24 ℃, the proton signal of H-4'x and H-4'y appears as a mean value at δ -0.22 because of a rapid flipping of the heptamethylene chain (Figure 2). The signal disappears at -10 ℃, and the signal of H-4'x in conformer (**A**) [or H-4'y in **B**] reappears at δ -1.50 as of 1H intensity with a clear coupling pattern at -50 ℃. The counterpart is expected to appear at δ 1.16, but it was hidden behind the signals of other aliphatic protons. These observations suggest that each of the geminal protons is located in a different environment and the flipping of the heptamethylene chain is frozen in the NMR time scale at -50 ℃. The energy barrier ($\Delta G^{\ddagger}_{c}$) of the conformational change between **A** and **B** of **10c** is 11.3 Kcalmol^{-1} (T_c, -10 ℃). The energy barriers of the conformational change between **A** and **B** of **16c** was also estimated similarly (Figure 2) to be 12.2 kcalmol^{-1} (T_c, -5 ℃). The

Table 1. Selected physical data of compounds (**10a-c**) and (**16a-c**)

10a: mp 52-53 ℃ (AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85-0.93 (2H, m), 0.95-1.00 (2H, m), 1.07-1.18 (6H, m), 1.59-1.83 (4H, m), 2.14 (2H, tt, J=6.5, 6.6 Hz), 2.66 (2H, t, J=6.6 Hz), 2.86, (2H, t, J= 6.5 Hz), 3.14 (2H, t, J=6.3 Hz, H-9'), 3.16 (2H, t, J= 6.3 Hz, H-1'), 7.12 (1H, s, H-3); UV λ_{max} (log ε) in EtOH 208 (4.19), 247 (3.85), 287 (3.67).

10b: oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.70-0.80 (4H, m), 1.12-1.14 (2H, m), 1.23-1.26 (2H, m), 1.59-1.67 (4H, m), 2.13 (2H, quint, J=6.5 Hz), 2.67 (2H, t, J=6.6 Hz), 2.80 (2H, t, J=6.2 Hz), 3.12 (2H, t, J=6.3 Hz, H-8'), 3.17 (2H, t, J=6.1 Hz, H-1'), 7.16 (1H, s, H-3); UV λ_{max} (log ε) in EtOH 210 (4.23), 247 (3.89), 287 (3.65).

10c: oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.22 (2H, br s), 1.35-1.55 (6H, m), 1.56-1.72 (2H, m), 2.13 (2H, quint, J=6.5 Hz), 2.67 (2H, t, J=6.6 Hz), 2.84 (2H, t, J=6.1 Hz), 3.10 (2H, t, J=6.2 Hz, H-7'), 3.20 (2H, br s, H-1'), 7.33 (1H, s, H-3); UV λ_{max} (log ε) in EtOH 215 (4.18), 249 (3.85), 292 (3.50).

16a: mp 59-62 ℃ (AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81-0.95 (4H, m), 1.03-1.24 (6H, m), 1.84-1.92 (4H, m), 3.04 (2H, t, J=6.4 Hz, H-9'), 3.17 (2H, dd, J=6.4, 6.6 Hz, H-1'), 7.36 (1H, s, H-3), 7.49 (1H, dd, J=8.1, 7.2 Hz), 7.67 (1H, dd, J=8.2, 7.1 Hz), 7.99 (1H, d, J=8.2 Hz), 8.07 (1H, d, J=8.4 Hz); δ_{av}=7.81; UV λ_{max} (log ε) in EtOH 230 (4.57), 280 (3.60), 305 (3.50), 318 (3.50).

16b: mp 64-65 ℃ (AcOEt) (lit.,[11] 64-66 ℃); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.60-0.66 (2H, m), 0.80-0.85 (2H, m), 1.10-1.26 (4H, m), 1.66-1.74 (4H, m), 2.99 (2H, dd, J=6.4, 6.5 Hz, H-8'), 3.11 (2H, dd, J=6.0, 6.2 Hz, H-1'), 7.38 (1H, s, H-3), 7.48 (1H, dd, J=7.9, 7.3 Hz), 7.67 (1H, dd, J=8.1, 7.2 Hz), 7.97 (1H, d, J=8.2 Hz), 8.06 (1H, d, J=8.4 Hz); δ_{av}=7.80; UV λ_{max} (log ε) in EtOH 229 (4.59), 278 (3.61), 306 (3.44), 3.19 (3.43).

16c: mp 43-46 ℃ (AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.46 (2H, br s), 1.27-1.70 (8H, m), 2.87 (2H, t, J=5.9 Hz, H-7'), 2.98-3.16 (2H, m, H-1'), 7.37 (1H, ddd, J=8.3, 6.8, 1.5 Hz), 7.45 (1H, s, H-3), 7.55 (1H, ddd, J=8.3, 6.8, 1.5 Hz), 7.86 (1H,, dd, J=8.6, 1.5 Hz), 7.93 (1H, d, J=8.3 Hz, 1.0); δ_{av}=7.68; UV λ_{max} (log ε) in EtOH 231 (4.58), 283 (3.59), 309 (3.39), 323 (3.36)

value for **10c** is similar to that of **4** (n=7) ($\Delta G^{\ddagger}_{c}$ 10.8 kcalmol^{-1}, T_c, -30 ℃)[13] and slightly smaller than that of 6-phenyl[7](2,4)pyridinophane (**3**) (n=7) ($\Delta G^{\ddagger}_{c}$ 12-13 kcalmol^{-1}; T_c,20 ℃).[12] The $\Delta G^{\ddagger}_{c}$ value of the quinolinophane (**16c**) was estimated for the first time and it is larger than that of **10c** but similar to that of **3** (n=7).[12]

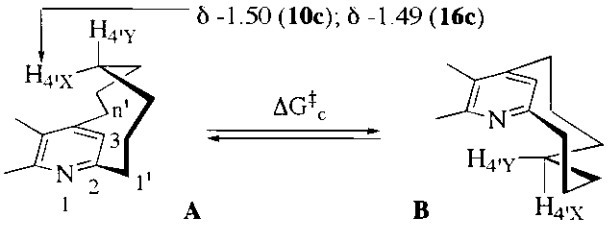


Figure 2 The flipping of the heptamethylene bridge of **10c** and **16c**

The ^{1}H NMR chemical shifts of aromatic protons are helpful in examining the distortion of the pyridine ring of pyridinophanes and quinolinophanes. The H-3 signals in **10a-c** and **16a-c** shift downfield as the methylene bridge becomes shorter. This feature is attributable to steric compression between H-3 and the methylene bridge.[12,13,18] It is remarkable that the average chemical shifts (δ_{av} in Table 1) of the protons on the fused benzene ring of quinolinophane (**16a-c**) exhibits a subtle high-field shift as the methylene bridge becomes shorter, probably because of the reduced ring current on the ring.

The deformation of the aromatic ring of cyclophanes and heterophanes is also evaluated by the red shift of the UV spectra.[12,13,19] The UV spectra of the series of pyridinophanes (**10a-c**) and quinolinophanes (**16a-c**) are summarized (Table 1). The ring strain of **10a-c** and **16a-c** is reflected in the red-shift as the value of [n] decreases. The longest absorption maxima of **10c** (n=7) and **16c** (n=7) are shifted by exactly 5 nm to longer wavelength than those of the corresponding compounds (**10a**) (n=9) and (**16a**) (n=9), both of which have a planar aromatic ring, respectively. Therefore, compound (**16c**) was clarified to contain the most deformed quinoline ring in the known [n](2,4)quinolinophanes.[10,11]

The basicity of amines is determined by the availability of the lone pair electron on the nitrogen. Only a few studies of the correlation between the base strength and deformation of the pyridine ring have been reported.[11,13] The basicities of **16a-c** [that is, the acidities (pK_a) of their conjugate acids] were determined to be **16a** (6.39), **16b** (6.44), and **16c** (6.54). These values are larger than those of 2-methylpyridine (5.92) and 2-methylquinoline (5.60), but smaller than that of 2,4-dimethylpyridine (6.72).[20] The results suggest that the deformation of the pyridine ring does not affect significantly the basicity, and the energy difference between the protonated and nonprotonated form becomes slightly larger as the methylene chain becomes shorter.

In summary, this work shows for the first time that easily accessible 3-amino-2-cyclohexenone reacts with 2-cycloalkenones to give [n](2,4)pyridinophane derivatives [n=9-7], which are converted to a series of [n](2,4)quinolinophanes [n=9-7]. Further study concerning the generality of the reaction is underway.

ACKNOWLEDGEMENT

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16. Elemental analyses and spectroscopic data are satisfactory for all new compounds in this paper.
17. Compound (**12**) was synthesized independently by using the thermal reaction of compound **5** with 1-nonen-3-one in xylene under reflux. For **12**: oil; δ_H ($CDCl_3$, 400MHz) 0.86-0.91 (3H, m), 1.28-1.42 (6H, m), 1.67-1.76 (2H, m), 2.19 (2H, quint, J=6.4 Hz), 2.67 (2H, t, J=6.6 Hz), 2.81 (2H, t, J=7.9 Hz), 3.12 (2H, t, J= 6.2 Hz), 7.13 (1H, d, J=8.1 Hz), 8.18 (1H, d, J=8.1 Hz).
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