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Synthesis, X-ray structure and NMR data of 12-amino-15-phenyl-2,5,8-trioxa-13-azabicyclo[9.2.2]pentadeca-1(14),12-diene-11,14-dicarbonitrile†

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Synthesis of unprecedented *oxygen-bridged* [*n*](2,5)pyridinophane dihydro-analogues

The development of new methods which allow the synthesis of [*n*]pyridinophanes and their dihydro-analogues is a major focus in supramolecular chemistry due to the many roles played by cyclophanes in biology and new technologies.[1] Pyridinophanes and their dihydro-analogues constituted the first examples of NADH models[2,3] capable of mimicking the diastereo-differentiating course of hydride exchange at pyridine dinucleotides under enzymatic conditions. In this way the asymmetric reduction of carbonyl substrates by optically active NADH model compounds has received wide attention.[3,4] Recently, crown ether annelated tetrathiafulvalenes were described as attractive components for sensor technology[5–7] and in some of these cases[6] pyridinophanes incorporating the tetrathiafulvalene (TTF) moiety have been studied as metal cations sensors.

In 1968 Gerlach and Huber[8] synthesized the first [*n*](2,5)pyridinophanes, *carbon-bridged* compounds, some *sulfur-bridged* [*n*](2,5)pyridinophanes were constructed and described as Vitamin B_6,[9] pyridoxal[10] and pyridoxamine[11] analogues; however, no synthetic procedure was reported to afford [*n*](2,5)pyridinophanes in which some methylene groups of the bridge were replaced by oxygen.

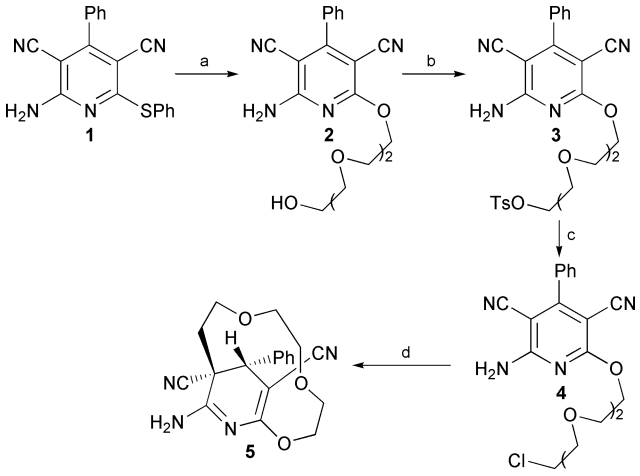
The synthesis of nearly all [*n*](2,5)pyridinophanes known has previously been accomplished using different synthetic strategies: (i) *via* the construction of the pyridine ring as happens in the acid-catalyzed cyclization of bis(β-aminovinyl)diketones[8] or (ii) by building the *ansa-chain* around the pyridine ring as in the thermal 1,6-Hofmann elimination from an intimate mixture of (4-methylbenzyl)trimethylammonium hydroxide and (5-methyl-2-picolinyl)trimethylammonium hydroxide.[12] *Sulfur-bridged* [*n*](2,5)pyridinophanes have been obtained through the Vögtle method by the condensation of dithiols with dihalogenopyridine compounds.[13]

Herein we present an unprecedented method for synthesis of dihydro-analogues of *oxygen-bridged* [*n*](2,5)pyridinophanes by a C–C bond formation between the pyridine ring and the ω-position of a chain. As a preliminary result we report here the synthesis and structural studies of the *oxygen-bridged* [9](2,5)pyridinophane‡ dihydro-analogues **5**.

Cyclic voltammetric data on the mercury cathode of the 2-amino-6-methoxy-4-phenylpyridine-3,5-dicarbonitrile[14] showed two peaks in the cathodic region at −1.88 and −2.20 V (*vs*. Ag/Ag^+),§ which make this compound susceptible to reduction by amalgam (Na·Hg).[15] On the basis of this behavior, we have developed a molecular system containing a latent nucleophilic pyridine ring moiety, switched on by electrochemical reduction, and an electrophilic center moiety linked by oxyethylene bridges. Pyridine derivative **4**, also having two reduction peaks at −1.88 and −2.20 V (*vs*. Ag/Ag^+),§ was chosen as a molecular model of this system. We have carried out its synthesis in multistep processes from pyridine **1**[16] as depicted in Scheme 1, *via* the substitution of the phenylthio group by triethylene glycol to afford **2** and followed by tosylation to **3** which could be converted in good yield to chloride **4**.

The synthesis of the *oxygen-bridged* [9](2,5)pyridinophane dihydro-analogues **5** was accomplished with an amalgam (Na·Hg) reduction of **4** in *N*,*N*-dimethylformamide under argon and required two eq. of Na per mol of **4**. The structure of **5** was well established by NMR spectroscopy,¶ X-ray diffraction study‖ and elemental analysis.

The structure of **5** can be clearly seen in the X-ray crystal structure (Fig. 1). Noteworthy structural features are the *trans* stereochemistry between the phenyl group on C15 and the *ansa-chain* bonding to the C11 atom, the very short distance C12–N20 (1.330 (4) Å) and sp^2 hybridization of N20.



Scheme 1 *Reagents and conditions*: (*a*) Under argon atmosphere, NaH (9 eq.), triethylene glycol (18 eq.), **1** (3 eq.), DMF, rt, 48 h, then poured on water, the precipitate was chromatographed (silica gel, CH_2Cl_2–EtOH, 25 : 1), 70%; (*b*) Under argon atmosphere, triethylamine (3.3 eq.), **2** (3 eq.) in dry CH_2Cl_2 (25 ml), 30 min, then toluene-*p*-sulfonyl chloride (3.3 eq.) in dry CH_2Cl_2 (10 ml) was added dropwise, rt, 12 h, then was neutralized with HCl (10%), solvent was removed *in vacuo* and the residue was chromatographed (silica gel, CH_2Cl_2–hexane, 25 : 1), 70%; (*c*) **3** (2 eq.), LiCl (8 eq.), dry MeOH (50 ml), reflux 4 d, purified by column chromatography (silica gel, CH_2Cl_2), 60%; (*d*) Under argon atmosphere, **4** (2 eq.), dry DMF (4 ml), amalgam (Na·Hg) (0.97% w.w. Na = 92 mg = 4 eq.), 0 °C, 24 h, then the solution was separated and evaporated to dryness and the residue was purified by column chromatography (neutral aluminium oxide, CH_2Cl_2–hexane, 20 : 1), 40%.

† Electronic supplementary information (ESI) available: 2D-J resolved ^1H spectra, 2D-COSY ^1H–^1H–^{13}C spectra of **5**. See http://www.rsc.org/suppdata/cc/b0/b004474l/

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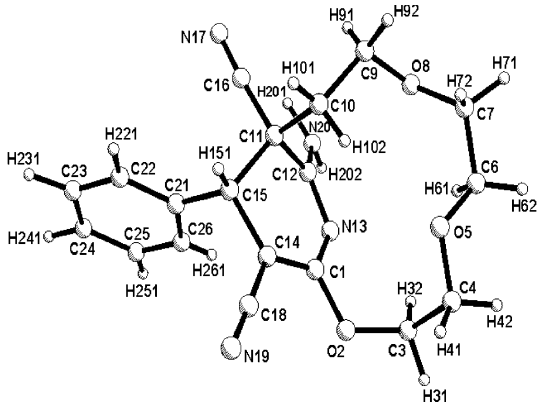

Fig. 1 View of the molecular structure of compound **5**. Selected bond lengths [Å] and angles [°]: C(1)–C(14) 1.343(5), C(1)–O(2) 1.352(4), C(1)–N(13) 1.369(4), C(11)–C(12) 1.524(5), C(11)–C(15) 1.564(4), C(12)–N(13) 1.298(4), C(12)–N(20) 1.330(4), C(14)–C(18) 1.411(5), C(14)–C(15) 1.523(4), C(15)–C(21) 1.517(4), N(13)–C(12)–N(20) 119.0(3), N(20)–C(12)–C(11) 119.0(3).

The ^{1}H NMR of **5**¶ shows two multiplets for the Ph ring, one singlet for the C15-H resonance and the three expected ABCD spin systems with typical values of SSCC for CH_2CH_2 groups of *ansa*-moiety, which were assigned by using the ^{1}H *J*-resolved, 2D-COSY ^{1}H–^{1}H and 2D-COSY ^{1}H–^{13}C spectra.† The observation of two unequivalent protons for the NH_2 group at δ = 8.5 and 7.8 ppm is due to very slow rotation around the C_{12}–N bond.

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Notes and references

‡ The IUPAC name for [9](2,5)pyridinophane is 12-azabicyclo[9.2.2]pentadeca-11,13,14-triene.

§ *Measurement of reduction potential.* The reduction potentials of the 2-amino-3,5-dicyano-6-methoxypyridine and **4**, were measured by means of cyclic voltammetry at 25 °C and at the scan rate of 0.2 V s^{-1} using a mercury cathode as the working electrode and Ag/AgCl as the reference electrode.

¶ *Selected data* for **5**: mp. 265–266 °C (from ethyl acetate–hexane, 15 : 1); ν_{max}(KBr)/cm^{-1} 3420, 3352, 2900, 2220 (*weak*), 2186, 1630, 1548, 1450, 1366, 1314, 1150, 1130, 702; δ_H(500 MHz, DMSO-d_6, 25 °C) 8.49 (1H, s, NH_2), 7.79 (1H, s, NH_2), 7.34 (3H, m, *meta*- and *para*-Ph), 7.15 (2H, m, *ortho*- Ph), 5.12 and 3.81 ($C3H_2$), 3.70 and 3.47 ($C4H_2$), 3.50, 3.27, 3.74 and 3.39 ($C6H_2C7H_2$), 3.76 and 3.64 ($C9H_2$), 2.77 and 2.02 ($C10H_2$), 3.82 (1H, s, C15H); δ_C(125 MHz, DMSO-d_6, 25 °C) 166.54 (m, C1), 62.59 (t, $^1J_{C\text{-}H}$ = 145.8 Hz, C3), 70.40 (t, $^1J_{C\text{-}H}$ = 140.8 Hz, C4), 70.41 and 71.94 (two t, $^1J_{C\text{-}H}$ = 140.8, 140.8 Hz, C6, C7), 67.89 (t, $^1J_{C\text{-}H}$ = 140.8 Hz, C9), 35.69 (t, $^1J_{C\text{-}H}$ = 134.6 Hz, C10), 44.25 (m, C11), 160.58 (tm, $^2J_{C\text{-}H}$ = 6.66 Hz, C12), 61.52 (d, $^2J_{C\text{-}H}$ = 6.2 Hz, C14), 46.05 (d, $^1J_{C\text{-}H}$ = 138.7 Hz, C15), 117.82 (dd, $^3J_{C\text{-}H}$ = 9.46, 3.05 Hz, C16), 119.67 (d, $^3J_{C\text{-}H}$ = 4.90 Hz, C18), 137.73, 127.96, 127.66 and 127.58 (*ipso*-, *meta*-, *ortho*-, *para*- of Ph ring); MS (CI) *m*/*z* 353 [M + H$^+$]; Anal. calc. for $C_{19}H_{20}N_4O_3$, C, 64.77, H, 5.68, N, 15.91. Found C, 64.95, H, 5.52, N, 16.15%.

‖ Crystals of **5**, suitable for X-ray crystallography grown from ethyl acetate. Crystal data of **5**. $C_{19}H_{20}N_4O_3$, M_t = 352.39, triclinic, space group $P\bar{1}$, a = 9.377(1), b = 9.409(1), c = 11.909(1) Å, α = 68.17(2), β = 84.5(1), γ = 60.62(2)°, V = 845.0(1)Å^3, T = 293 K, Z = 2, μ($Mo_{K\alpha}$) = 0.096 mm^{-1}; 3225 measured reflections, 2976 were independent; $R1$ = 0.056 and $wR2$ = 0.118 (for 1623 reflections with $F > 4\sigma(F)$).

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