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The Spontaneous Cyclodimerization of 2,3-Dihydroisoquinolines after Base Promoted Elimination of Methanol from 4-Methoxy-1,2,3,4-tetrahydroisoquinolines

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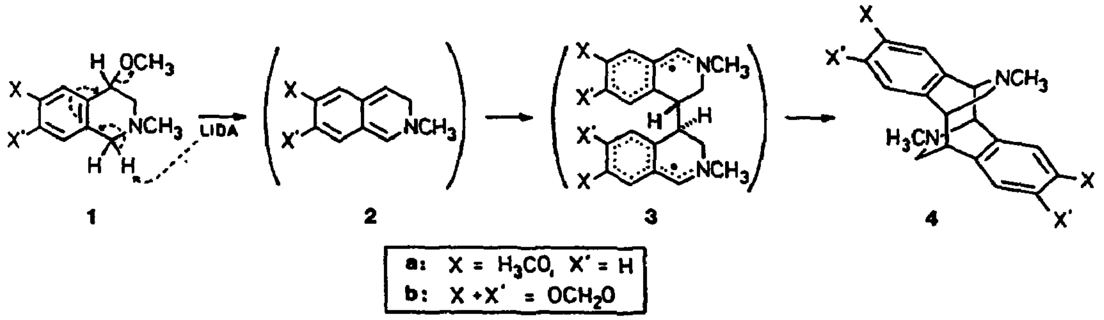
Abstract: *The reaction of 4-methoxy-1,2,3,4-tetrahydroisoquinolines 1 with lithium diisopropylamide affords dimerization products 4. The intermediacy of orthoquinodimethanes 2 and diradicals 3 is assumed.*

Site selectivity of organometallic attack can be advantageously exploited in the synthesis of peculiarly substituted isoquinolines. In continuation of our systematic investigations [1] we have studied the deprotonation of 4-methoxy-1,2,3,4-tetrahydroisoquinolines 1. Addition of an ethereal (5 mL) solution of compound 1a [2] (5 mmol) to a solution of lithium diisopropylamide (20 mmol) in tetrahydrofuran (10 mL) afforded the dimerization product 4a (74 %) in the course of 10 minutes. A similar treatment of compound 1b with lithium diisopropylamide gave dimer 4b (74 %) [3].



The dimer structures 4 have been assigned on the basis of spectral data [4]. The ^{13}C-NMR spectrum showed five aliphatic carbon signals as required by the symmetry of the product. In perfect agreement with the postulated head-to-head structure, the ^{1}H-NMR spectra show two different bridgehead hydrogen atoms, *both as singlets*. The *exo* structure (*i.e.*, the benzo rings pointing in different directions) follows from the up-field shift of the *N*-methyl resonance of dimers 4 when compared with that of the precursors 1. The structure of dimer 4a was confirmed by single crystal X-ray diffraction [5].

The formation of dimers 4 can be rationalized by assuming a lithium diisopropylamide promoted elimination of methanol and the subsequent dimerization of the resulting 2,3-dihydroisoquinoline 2 providing dimers 4. Intermediate 2 is a cyclic analogue of orthoquinodimethanes. The syntheses and reactions of orthoquinodimethanes have been reviewed [6]. The lithium diisopropylamide promoted 1,4-elimination of methanol from methyl *o*-methylbenzyl ether, generating *o*-phenylenedimethane, has been described [7]. Head-to-head dimerizations of orthoquinodimethanes are known and, in one case, a stepwise mechanism involving a diradical intermediate (such as 3) has been suggested [8].

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[2] Compounds 1 were prepared by refluxing the corresponding 4-hydroxiisoquinoline (0.1 mol) in a mixture of methanol (200 mL) and concentrated hydrochlorid acid (20 mL) for 30 h; 1a: bp 105 - 110 °C (0.1 mmHg), 1b: mp 62 - 63 °C.

[3] 4a: mp 198 - 199 °C (ethyl acetate), 4b: mp 260 - 261 °C (*N,N*-dimethylformamide).

[4] 4a: ^{1}H-NMR (250 MHz, $CDCl_3$): δ 7.06 (2 H, d *J* 8.8), 6.7 (4 H, m), 4.10 (2 H, s), 3.83 (6 H, s), 3.30 (2 H, s, broad), 2.95 (2 H, d, *J* 10.5), 2.03 (2 H, dm, *J* 10.5), 2.00 (6 H, s).
^{13}C-NMR (62.9 MHz, $CDCl_3$): 157.8 (s), 142.2 (s), 132.5 (s), 127.7 (d, *J* 154), 114.1 (d, *J* 157), 10.2 (d, *J* 156), 70.5 (d, *J* 137), 55.3 (q, *J* 143), 55.1 (t, *J* 137), 46.2 (q, *J* 133), 42.5 (d, *J* 131).
4b (dihydrochloride): ^{1}H-NMR (250 MHz, D_2O): δ 7.26 (2 H, s) 7.15 (2 H, s), 6.18 (2 H, s), 6.14 (2 H, s), 5.30 (2 H, s), 4.01 (2 H, s, broad), 3.74 (2 H, d, *J* 13.5), 2.84 (2 H, d, *J* 13.5, broad), 2.67 (5 H, s).

[5] Compound 4a, $C_{22}H_{26}N_2O_2$, crystallized from ethyl acetate in the monoclinic system with unit cell dimensions a = 10,481(1), b = 11,897(1), c = 15,254(1) Å, b = 106,37(1)°, V = 1825,0 Å^3. Space group C2/c. Intensity data were collected on an Enraf Nonius CAD4 diffractometer. The structure was solved by direct methods and refined on F^2 values to $R[F^2>2\sigma(I)] = 0.053$ for 3804 observations: A. Kálmán, Gy. Argay, *Acta. Cryst. C*, to be published.

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