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NEW DIMERS FROM THE DECOMPOSITION OF α-LITHIO-*N*-NITROSAMINES. EVIDENCE FOR NO$^{\bullet}$ ELIMINATION.

Pelayo Camps*, Jesús Maldonado, David Mauleón, Cristina Minguillón, and María Dolores Pujol

Laboratorio de Química Farmacéutica, Facultad de Farmacia, Universidad de Barcelona. Av. Diagonal, s/n, 08028 Barcelona (Spain)

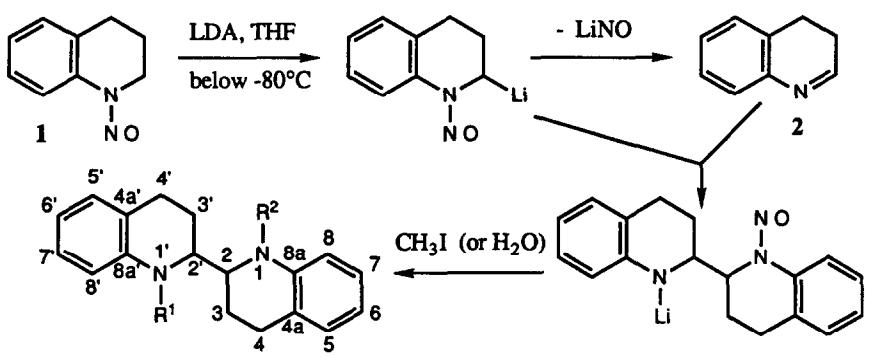
SUMMARY. Reaction of N-nitroso-1,2,3,4-tetrahydroquinoline (1) with LDA in THF at temperatures below -80°C followed by reaction with methyl iodide or quenching with water gave, among other products, 1'-methyl-1-nitroso-1,1',2,2',3,3',4,4'-octahydro-2,2'-biquinoline (3) and its 1'-demethyl derivative (4), respectively, through the possible intermediacy of 3,4-dihydroquinoline (2).

The α-metallation of activated derivatives of secondary amines is a matter of active synthetic interest.[1] The synthetic application of α-lithio-*N*-nitroso-*N*,*N*-dialkylamines is well established.[1c,d] These α-metalloamines should be generated and manipulated at very low temperatures (below -80°C) since they tend to dimerize to 1,4,5,6-tetrahydrotetrazine 2-oxide derivatives.[1d] Although the reaction of *N*-nitrosamines with bases such as sodium hydride[2] or potassium amide[3] is known to give imines through HNO elimination, no unequivocal evidence of such a process has been obtained so far in the α-lithiation of *N*-nitroso-*N*,*N*-dialkylamines.[1d] Transnitrosation reactions have been observed in the α-lithiation of *N*-nitroso-*N*-alkylanilines. Moreover, from α-lithio-*N*-nitroso-*N*-methylaniline, *N*,*N'*-dinitroso-*N*,*N'*-diphenylethylenediamine and *N*,*N'*-diphenylethylenediamine were isolated. Seebach and Enders[1d] considered that these compounds, like the tetrazine-*N*-oxide dimers, are formed by C-C linkage between the formerly anionic C-atoms of the lithionitrosamines, pointing out that the dinitroso-derivative is a dimer minus H_2 of the original nitrosamine.

In connection with an improved synthesis of 3,3a,4,5,-tetrahydropyrazolo[2,3-a]quinoline-2-amine,[4] a potential antiinflammatory agent, we studied the reaction of 2-lithio-1-nitroso-1,2,3,4-tetrahydroquinoline with alkylating agents. Reaction of **1** with LDA in anhydrous THF at -96°C followed by reaction with methyl iodide gave, after standard work-up and column chromatography (silica gel, hexane-ethyl acetate as eluent), a compound whose elemental analysis was concordant for $C_{19}H_{21}N_3O$, that was characterized[5] as 1'-methyl-1-nitroso-1,1',2,2',3,3',4,4'-octahydro-2,2'-biquinoline (**3**) (26% yield), as the only defined reaction product.

In the same way, after quenching the solution of 2-lithio-**1** with water, we obtained a solid compound that was characterized[5] as 1-nitroso-1,1',2,2',3,3',4,4'-octahydro-2,2'-biquinoline (**4**) (13% isolated yield).[6] Compounds **3** and **4** have two chiral centers, and two racemic pairs are possible in each case. However, the isolated compounds correspond to only one racemic mixture. Since **3** must be formed by methylation of the lithium salt of **4**, it seems reasonable that both compounds have the same relative configuration. Hydrolysis of compound **4** (HCl / benzene)[7] gave the symmetric 1,1',2,2',3,3',4,4'-octahydro-2,2'-biquinoline (**5**),[8] which seems to be the *meso*-stereoisomer.[9] Thus, compounds **3** and **4** must be the *erythro* racemic pairs. Compound **5** has been identified also as a by-product formed from the lithio derivative of **1** on quenching with water.

It is worthy of note from their ^1H NMR spectra, the high value of the coupling constant $J_{H2,H2'}$ in **3** (9.2 Hz) and **4** (9.0 Hz) showing the preferred conformation around the C2-C2' bond to be one in which the hydrogen atoms are in an *anti* arrangement. The fact that both coupling constants $J_{H2,H3\alpha}$ and $J_{H2,H3\beta}$ in **3** and **4** are small is indicative of an "envelope-like" conformation with *axial* 2-substituent for their *N*-nitroso-heterocyclic moiety.[1d] A similar situation is found for the *N*-methyl-heterocyclic part of **3**. However, in the case of **4**, the N-H ring, free of steric interactions between substituents at the 1' and 2' positions, seems to exist preferentially in a conformation with equatorial 2'-substituent. One of the $J_{H2',H3'}$ values (9.0 Hz) must be associated to an *anti* arrangement for the corresponding protons.



3, $R^1 = CH_3$, $R^2 = NO$
4, $R^1 = H$, $R^2 = NO$
5, $R^1 = R^2 = H$

Scheme 1

The formation of compounds **3** and **4** in these reactions can be easily explained as shown in Scheme 1, by NO^- elimination from the α-lithio-**1**, with formation of 3,4-dihydroquinoline (**2**), which on reaction with lithiated **1** will give the *N*-lithio-**4**, from which **3** and **4** derive. The formation of the dimers obtained by Seebach and Enders[1d] from α-lithio-*N*-nitroso-*N*-methylaniline can be similarly explained. All these observations constitute evidence for the decomposition of the lithio-derivatives of *N*-nitroso-*N*-alkylanilines via NO^- elimination.

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5. *Significative physical and spectroscopic data of compounds 3, 4 and 5.* Assignment of the ^1H NMR spectra of **3** and **4** were carried out on the basis of the chemical shifts and coupling constants obtained with the aid of double-resonance and phase-sensitive homocorrelation experiments. The ^{13}C NMR spectra of **3** and **4** were assigned taking into account their chemical shift, type of carbon atom (DEPT) and, in the case of **3**, by one bond and long range two-dimensional $^1H,^{13}C$ heterocorrelation experiments.

Compound **3**: mp 143-145°C (anh. acetone); IR ($CHCl_3$), n 3400 (N-H st) and 1450 (N=O st) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$), d 1.6-2.1 (m, 4H, 3-H_2 and 3'-H_2), 2.6 (s, 3H, NCH_3), 2.7-3.1 (m, 4H, 4-H_2 and 4'-H_2), 3.53 (dt, J = 9.2 Hz, J' = 4.0 Hz, 1H, 2'-H), 5.52 (dt, J = 9.2 Hz, J' = 4.6 Hz, 1H, 2-H), 6.40 (dd, J = 7.8 Hz, J' = 1.2 Hz, 1H, 8'-H), 6.63 (dt, J = 1.2 Hz, J' = 7.2 Hz, 1H, 6'-H), 7.00 (dd, J = 7.2 Hz, J' = 1.6 Hz, 1H, 5'-H), 7.08 (dt, J = 1.6 Hz, J' = 7.2 Hz, 1H, 7'-H), 7.2-7.4 (m, 3H, 5-H, 6-H, and 7-H), 7.93 (dm, J = 7.0 Hz, 1H, 8-H); ^{13}C NMR (50.3 MHz, $CDCl_3$), d 22.5 (C-3 or C-3'), 22.9 (C-3' or C-3), 23.2 (C-4 or C-4'), 23.6 (C-4' or C-4), 39.2 (CH_3), 48.6 (C-2), 57.6 (C-2'), 111.3 (C-8'), 116.1 (C-6'), 118.0 (C-8), 120.5 (C-4a'), 126.1 (C-4a), 126.5 (C-6), 127.3 (C-7'), 127.7 (C-5 or C-7), 128.6 (C-5'), 129.4 (C-7 or C-5), 137.4 (C-8a), 144.6 (C-8a'); MS (chemical ionization, NH_3), m/z 308 ($M^+ + 1$, 100%), 278 ($M^+ + 1 - NO$, 49%).

Compound **4**: mp 158-161°C (anh. acetone); IR (KBr), n 1460 (N=O st) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$), d 1.6-2.3 (m, 4H, 3-H_2 and 3'-H_2), 2.7-3.1 (m, 5H, 4-H_2, 4'-H_2, and NH), 3.42 (dt, J = 3.2 Hz, J' = 9.0 Hz, 1H, 2'-H), 5.40 (ddd, J = 3.8 Hz, J' = 4.8 Hz, J'' = 9.0 Hz, 1H, 2-H), 6.37 (dd, J = 7.9 Hz, J' = 1.1 Hz, 1H, 8'-H), 6.60 (dt, J = 1.1 Hz, J' = 7.4 Hz, 1H, 6'-H), 6.9-7.0 (m, 2H, 5'-H and 7'-H), 7.2-7.4 (m, 3H, 5-H, 6-H, and 7-H), 7.97 (dm, J = 6.8 Hz, 1H, 8-H); ^{13}C NMR (50.3 MHz, $CDCl_3$), d 22.4 (C-3 or C-3'), 23.1 (C-4 or C-4'), 24.3 (C-3' or C-3), 25.6 (C-4' or C-4), 50.9 (C-2'), 51.1 (C-2), 114.7 (C-8'), 117.5 (C-6'), 118.1 (C-8), 120.5 (C-4a'), 126.1 (C-4a), 126.8 (C-6 and C-7'), 127.6 (C-5 or C-7), 128.9 (C-5'), 129.5 (C-7 or C-5), 136.8 (C-8a), 143.5 (C-8a'); MS (electron impact), m/z 293 (M^+, 1%), 132 ($C_9H_{10}N^+$, 100%).

Compound **5**: mp 112-114°C (methanol); IR ($CHCl_3$), n 3425 (N-H st) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$), d 1.7-2.1 (m, 4H, 3-H_2 and 3'-H_2), 2.77 (m, 4H, 4-H_2 and 4'-H_2), 3.27 (m, 2H, 2-H and 2'-H), 3.6 (ba, 2H, 2NH), 6.5-6.6 (m, 4H, 6-H, 6'-H, 8-H, and 8'-H), 6.9-7.1 (m, 4H, 5-H, 5'-H, 7-H, and 7'-H); ^{13}C NMR (50.3 MHz, $CDCl_3$), d 23.9 and 25.6 [C-3(3') and C-4(4')], 54.6 [C-2(2')], 114.8 [C-8(8')], 117.5 [C-6(6')], 121.7 [C-4a(4a')], 127.0 [C-7(7')], 129.3 [C-5(5')], 144.2 [C-8a(8a')]; MS (electron impact), m/z 264 (M^+, 3.2%), 133 ($C_9H_{11}N^+$, 49%), 132 ($C_9H_{10}N^+$, 100%), 130 ($C_9H_8N^+$, 44%).

6. Compound **4** seems to be the major reaction product. However, it is difficult to isolate in pure state since it decomposes on standing.

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8. A synthesis of compound **5** by Zn/Ac_2O reduction of quinoline followed by hydrogenation and hydrolysis, has been claimed.[10] However, in this publication, no NMR data are presented and the stereoisomeric composition of the product is not established. In our hands, this process gave a complex mixture of reduction products, and thus, no comparison is possible.

9. Spectroscopic (IR, ^1H and ^{13}C NMR, and CG/MS) and HPLC (methanol, acetonitrile, or acetonitrile:water/9:1, as eluents; UV detection at different wave-length) analyses of this compound showed to be majorly (> 95%) a single compound not resolved by HPLC using a chiral column [(+)-poly(triphenylmethylmethacrilate), 25x0.46 cm internal diameter, (+)-OT from Daicel Co. (Japan), λ = 254 nm, methanol as eluent].

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