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Alternative Syntheses of Bridgehead Polycyclic 1,2-Diamines and 2-Aminoalcohols from Di- and Mono-oximes of Some Bicyclic Diketones: Highly Improved Synthesis of Tricyclo[3.3.1.$0^{3,7}$]nonane-3,7-diamine.

Pelayo Camps* and Diego Muñoz-Torrero

Laboratorio de Química Farmacéutica, Facultad de Farmacia, Universidad de Barcelona, Av. Diagonal s/n; E-08028 Barcelona, Spain

Abstract: *Bridgehead polycyclic 1,2-diamines **4a** and **4b** have been obtained from dioximes **2a** and **2b**, respectively, by two alternative procedures: a) m-chloroperbenzoic acid oxidative coupling to **3a** and **3b**, followed by reduction with aluminum amalgam, and b) reductive coupling with aluminum amalgam. Similarly, the related 2-aminoalcohols **9a** and **9b** have been obtained from the corresponding monooximes **7a** and **7b**.*

In connection with the preparation of lipophilic rigid acetylcholine-like compounds we required bridgehead polycyclic 1,2-diamines and 2-aminoalcohols, such as **4** and **9**, which otherwise are compounds of potential interest as ligands for organometallic complexes[1] and intermediates for pharmaceuticals[2]. Although diamine **4a** is a known compound[1], its synthesis implies nine steps from diethyl malonate, the last one, i.e., the Schmidt degradation of tricyclo[3.3.1.$0^{3,7}$]nonane-3,7-dicarboxylic acid, giving only 13.4% yield of **4a**.

First, we envisioned the preparation of **4a** by reduction of the known dinitro compound **3a**[3] (Scheme 1). Reaction of a mixture of *syn*- and *anti*-dioximes **2a** with *m*-chloroperbenzoic acid following the method of Paquette for a related case[4] gave **3a** in 59% yield. This compound was also obtained by $NaBH_4$ reduction of *exo*-3,*exo*-7-dibromo-*endo*-3,*endo*-7-dinitrobicyclo[3.3.1]nonane,[3] although in 11% overall yield from **2a**.

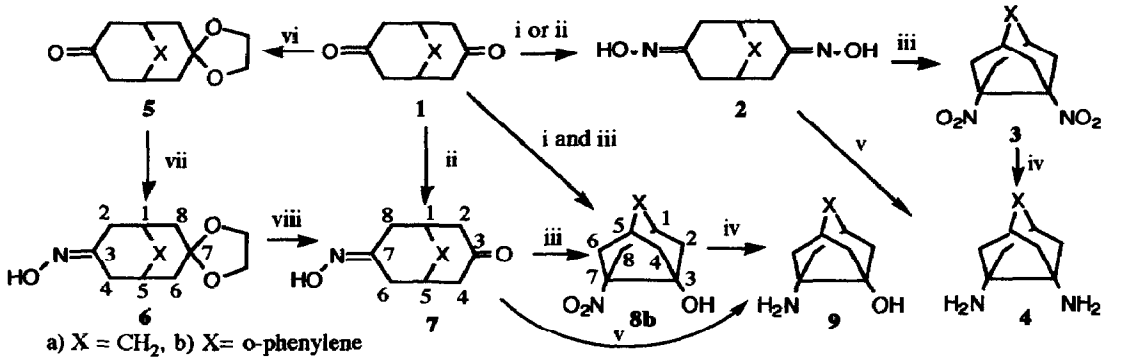
The reduction of **3a** to **4a** was a difficult task. Catalytic hydrogenation using different catalysts (10% Pd on charcoal[5] or PtO_2[6]) and reaction conditions (medium pressure, neutral or acidic medium) gave complex mixtures of products not containing **4a**. Similarly, reductions carried out with metal hydrides such as $NaBH_4$ / 10% Pd on charcoal,[7] $LiAlH_4$[8] or nickel boride / $NaBH_4$[9] or metals in protic solvents such as Fe / acetic acid[10] or Sn / conc. HCl[11] failed, in spite of the fact that the last conditions had been successfully used to reduce *vicinal tert*-dinitro compounds. Finally, we were able to carry out cleanly this reduction by using aluminum amalgam[12] in mixtures THF/ methanol / H_2O under sonication, isolating **4a** as a white solid in 75% yield.[13]

Next, in order to avoid the redundance of the above sequence (oxidation / reduction) we tried the direct conversion of **2a** to **4a**. Reduction of **2a** with aluminum amalgam in a mixture ethanol / H_2O under sonication gave **4a** in 77% yield.[14] Thus, this transformation represents the simplest way to obtain **4a**, clearly superior to the previously described[1a] and the two-step one herein first reported.

Similarly, diamine **4b** was obtained from dioxime **2b** by the two above described alternative procedures : a) oxidative coupling with *m*-chloroperbenzoic acid to **3b** (68% yield) followed by aluminum amalgam reduction (89% yield) and b) reductive coupling with aluminum amalgam (84% yield).[15]

The application of these procedures to the preparation of tricyclo[3.3.0.$0^{3,7}$]octane-1,5-diamine or its 3,7-dimethyl-derivative failed. Oxidation of *cis*-bicyclo[3.3.0]octane-3,7-dione, dioxime (**2**, X = bond) and its 1,5-dimethyl-derivative led to stereoisomeric mixtures of the corresponding bicyclic dinitro compounds, while

reduction of these dioximes with aluminum amalgam under sonication gave stereoisomeric mixtures of the corresponding bicyclic diamines. These facts can be explained on the basis of the distance between the carbon atoms to be coupled in these bicyclo[3.3.0]octane-derivatives and the strain of the corresponding tricyclic skeleton.[16]



a) X = CH_2, b) X= o-phenylene

i) $NH_2OH.HCl/NaOAc/H_2O$, 40°C; ii) $NH_2OH.HCl$/Anh. $BaCO_3$/Dioxane, Δ; iii) *m*-chloroperbenzoic acid /acetonitrile/Na_2HPO_4/urea; iv) Al-Hg/Methanol/THF/H_2O, sonication; v) Al-Hg/Ethanol/H_2O, sonication; vi) Ethyleneglycol/Toluene/*p*-TsOH, Δ; vii) $NH_2OH.HCl$/ Anh. $BaCO_3$/Ethanol, Δ; viii) H_2SO_4/Methanol, Δ.

Scheme 1

To prepare aminoalcohols **9** by using the above reductive coupling, monooximes of diketones **1** were required. Monooxime **7a** was prepared from diketone **1a**, in 66% overall yield, by monoacetalization[17] with ethyleneglycol, followed by reaction with $NH_2OH.HCl$ and anhydrous $BaCO_3$ in absolute ethanol to give acetal oxime **6a**, and hydrolysis with H_2SO_4 in methanol. Reduction of **7a** with aluminum amalgam in a mixture ethanol / water under sonication gave aminoalcohol **9a** in 80% yield. Aminoalcohol **9a** was also prepared, although in lower yield (22%), by aluminum amalgam reduction of a crude mixture obtained from the reaction of diketone **1a** with one equivalent of hydroxylamine in water.

Although we were able to prepare acetal oxime **6b** by using the same conditions used for **6a**, we could not obtain pure monooxime **7b** by hydrolysis. Reaction of diketone **1b** with 1 equivalent of hydroxylamine and anhydrous $BaCO_3$ in dry dioxane gave a mixture of starting diketone, mono-oxime **7b** and dioxime **2b**. Reduction of this mixture with aluminum amalgam gave a mixture of the corresponding products of reductive coupling (pinacol, aminoalcohol **9b** and diamine **4b**), from which **9b** was isolated in 30% overall yield. Alternatively, reaction of diketone **1b** with excess of hydroxylamine in water gave a complex mixture of products containing some dioxime **2b** plus other mono- and di-reaction products. Oxidation of this crude mixture with *m*-chloroperbenzoic acid let us isolate after column chromatography, nitroalcohol **8b** in 55% overall yield and dinitro compound **3b** in 20% overall yield. Aluminum amalgam reduction of **8b** in a mixture THF/ methanol / H_2O gave aminoalcohol **9b** in 94% yield.

Although, several synthesis of 1,2-diamines by reductive coupling of imines are known,[18] to the best of our knowledge, there is only one report on the reductive coupling of aromatic ketoximes to 1,2-diamines by using low valent titanium.[19] Intermolecular coupling of O-alkylated oximes with carbonyl compounds to O-alkyl-N-(2-hydroxyethyl)hydroxylamines has been accomplished by electroreduction[20] or with SmI_2[21]. Thus, this is the first report of a reductive coupling of aliphatic bis-ketoximes to 1,2-diamines and of monooximes of diketones to 2-aminoalcohols and, even though, the reaction works only in specially favoured intramolecular processes, its synthetic utility is evident.

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13. *General procedure for aluminum amalgam reduction of nitro-compounds.* A mixture of aluminum amalgam [from finely cut aluminum foil (260 mmol) and 2% aqueous $HgCl_2$ (15 mmol)] and the compound to be reduced (7 mmol) in a mixture of THF (120 ml) and 10% aqueous methanol (200 ml) is irradiated in an ultrasound bath for 12 h. The mixture is filtered, the solid is efficiently washed with diethyl ether, the combined filtrate and washings are concentrated in vacuo, diluted with water (10 ml) and extracted with CH_2Cl_2 (5 x 70 ml). After drying, the solution is concentrated to give the product.
14. *General procedure for aluminum amalgam reduction of mono- or dioximes.* A procedure and work-up similar to that described above is followed, using as solvent, a mixture of ethanol (53 ml) and water (13 ml) per mmol of compound stirring being continued magnetically for 12 h more, after ultrasound irradiation.
15. *Physical and spectroscopic data of the new compounds and 4a:*
All new compounds showed correct elemental analysis (C, H and N ± 0.3%). For the ^1H NMR and ^{13}C NMR data see Tables 1 and 2. The assignment of the NMR data of compounds **4a**, **5b**, **6a**, **6b**, **7a** and **8b** were carried out with the aid of the corresponding homocorrelation H-H and heterocorrelation H-C spectra.
3b, 7,8-Dinitro-5,6,7,8,9,10-hexahydro-5,8:7,10-dimethanebenzocyclooctene [m.p. 318°C (dec.) (CH_2Cl_2)]: IR (KBr) 1552, 1348 cm^{-1}. MS (CI, NH_3) m/e(%): 309(M^+ + 35, 68), 292(M^+ + 18,100).
4a [m.p. 183-185°C (acetonitrile)]: IR(KBr) 3425, 3342, 3277 cm^{-1}.
4b, 5,6,7,8,9,10-Hexahydro-5,8:7,10-dimethanebenzocyclooctene-7,8-diamine [m.p. 139-141°C (sublimed at 130°C/1 Torr)]: IR (KBr) 3328, 3268, 3178 cm^{-1}.
5b, 11,11-Ethylenedioxy-6,7,8,9-tetrahydro-5,9-propane-5H-benzocyclohepten-7-one, [m.p. 116-118°C (ethyl acetate)]: IR (KBr) 1681 cm^{-1}.
6a, 7,7-Ethylenedioxybicyclo[3.3.0]nonan-3-one, oxime [m.p.127-128°C(acetonitrile]. IR(KBr) 1653 cm^{-1}.
6b, 11,11-Ethylenedioxy-6,7,8,9-tetrahydro-5,9-propane-5H-benzocyclohepten-7-one, oxime [m.p. 176-178°C (isopropanol)]: IR(KBr) 3495, 3457, 1636 cm^{-1}.
7a, 7-Hydroxyiminobicyclo[3.3.0]nonan-3-one [m.p. 200-202°C(ethanol)]: IR(KBr) 3469,1687,1638 cm^{-1}.
8b, 8-Nitro-5,6,7,8,9,10-Hexahydro-5,8:7,10-dimethanebenzocycloocten-7-ol [m.p.157-162°C(CH_2Cl_2)]: IR (KBr) 3369, 1539, 1361 cm^{-1}. MS(CI, NH_3): m/e (%): 280(M^+ + 35, 100), 263(M^+ + 18, 87).
9a, 7-Aminotricyclo[3.3.1.$0^{3,7}$]nonan-3-ol [m.p. 210-211°C ($CHCl_3$)]: IR (KBr) 3333, 3274, 3148 cm^{-1}.
9b, 8-Amino-5,6,7,8,9,10-Hexahydro-5,8:7,10-dimethanebenzocycloocten-7-ol [m.p.144-148°C (sublimed at 110°C/0'3 Torr)]: IR (KBr) 3324, 3281, 3175 cm^{-1}. GC/MS (EI) m/e(%): 216(14), 215(M^+, 74), 198(M^+-OH, 18), 170(18), 158(44), 157($C_{11}H_9O^+$, 64), 156($C_{11}H_{10}N^+$, 100), 144(22), 143(26), 141(23), 131(11), 130(26), 129(43), 128(42), 127(18), 117(10), 116(15), 115(55), 96(11), 91(16), 78(11), 77(20), 65(11), 63(11), 58(31), 57(20), 56(11), 51(13), 44(11), 43(45), 42(52).
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Table 1. ^{13}C NMR (50.4 MHz, $CDCl_3$) Chemical Shifts[a] of the New Compounds and **4a**.

Comp.	C-1 C-5	C-2 C-4	C-3	C-6 C-8	C-7	X(CH_2	ar-C	ar-CH)		O-CH_2CH_2-O	
3b	43.6	47.2	101.7	47.2	101.7		141.6	127.8	129.9		
4a	33.2	50.9	60.6	50.9	60.6	32.6					
4b	42.6	50.6	65.7	50.6	65.7		144.5	125.9	129.0		
5b	38.6	47.1	209.5	40.2	110.5		143.9	127.4	128.3	63.3	64.5
6a	26.8*	35.1	157.6	40.2#	107.4	31.9				63.3	64.6
	28.0*	29.6		40.7#							
6b	38.2*	38.2	159.4	39.8#	110.5		143.5+	126.9≠	128.4≠	63.7	64.1
	38.8*	31.1		40.1#			143.7+	127.0≠	128.4≠		
7a	30.6*	46.8#	209.6	30.2	154.9	32.2					
	32.2*	47.1#		38.1							
8b	42.6	48.7	89.8	45.9	99.6		142.8	127.1	129.6		
9a	34.0	50.1*	77.9	50.7*	59.9	32.9					
9b	42.6	50.0*	82.4	50.3*	65.1		144.2	126.2	129.2		

[a] All these spectra have been taken at 50.4 MHz in $CDCl_3$. For equivalent carbon atoms, only the lowest numbered is indicated. See scheme 1 for the numbering. Absorptions from the same compound marked with *, #, + or ≠ can be interchanged.

Table 2. ^1H NMR Chemical Shifts[a] of the New Compounds and **4a**.

Compound	H-1 H-5	H-2exo H-4exo	H-2endo H-4endo	H-6exo H-8exo	H-6endo H-8endo	X(CH_2	ar-H)	NH_2/OH	O-CH_2CH_2-O	
3b[b,c]	3.61	2.27	3.31				7.21			
4a[d]	2.14	1.79	1.65			1.48		1.76		
4b[e]	3.03	1.99 - 1.99		1.99 - 1.99			7.10	1.49		
5b[f]	3.18	2.54	2.95	1.98	2.10		7.18		3.86	4.00
6a[g]	2.31	2.43	2.51	1.70 - 1.85		1.66		5.00	3.80	3.94
	2.31	2.19	3.06							
6b[h]	3.23	2.56	2.91	2.02 - 2.11			7.13	--	3.76	3.88
	3.23	2.44	3.43	2.02 - 2.11						
7a[i]	2.58*	2.47#	2.38	1.93	3.35	2.01		7.40		
	2.64*	2.38#	2.38	2.38	2.38					
8b[j]	3.40	2.13	2.39	2.06	3.35		7.17	2.51		
9a[e]	2.14	1.55 - 1.90		1.55 - 1.90		1.39		2.42		
9b[e]	3.08	1.97 - 2.25		1.97 - 2.25			7.10	2.61		

[a] Except where otherwise stated, the spectra have been taken at 500 MHz in $CDCl_3$. For equivalent protons, only the lowest numbered is indicated. See scheme 1 for the numbering. Absorptions from the same compound marked with * or # can be interchanged. [b] This spectrum was taken at 200 MHz in $CDCl_3$ + CD_3OD). [c] J(H-1,H-2exo) ~ 0 Hz, J(H-1,H-2endo) = 6.2 Hz, J(H-2exo,H-2endo) = 12.5 Hz. [d] J(H-2exo,H-2endo) = 10.0 Hz. [e] This spectrum was taken at 200 MHz. [f] J(H-1,H-2exo) = 5.5 Hz, J(H-1,H-2endo) = 3.0 Hz, J(H-2exo, H-2endo) =18.5 Hz, J(H-2exo, H-8exo) = 1.5 Hz, J(H-5,H-6exo) ~ 0 Hz, J(H-5,H-6endo) = 6.0 Hz, J(H-6exo,H-6endo) = 14.0 Hz. [g] J(H-1,H-2exo) = 6.5 Hz, J(H-1,H-2endo) ~ 0 Hz, J(H-2exo,H-2endo) = 17.0 Hz, J(H-4exo,H-4endo) = 18.0 Hz, J(H-4exo,H-5) = 7.5 Hz. [h] J(H-1,H-2exo) = J(H4exo,H-5) = 5.0 Hz, J(H-1,H-2endo) = J(H-4endo,H-5) = 4.0 Hz, J(H-2exo,H-2endo) = 15.5 Hz, J(H-4exo,H-4endo) = 16.0 Hz. [i] J(H-5,H-6exo) = 5.0 Hz, J(H-5,H-6endo) ~ 0 Hz, J(H-6exo,H-6endo) = 14.5 Hz. [j] J(H-1,H2exo) = J(H-5,H6exo) = 2.0 Hz, J(H-1,H2endo) = J(H-5,H6endo) = 6.5 Hz, J(H2exo,H2endo) = 12.5 Hz, J(H6exo,H6endo) = 12.0 Hz.

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