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A Surprising Eight-Membered Ring Synthesis Leading To Enantiomerically Pure Tricyclic Benzodiazepine Derivatives

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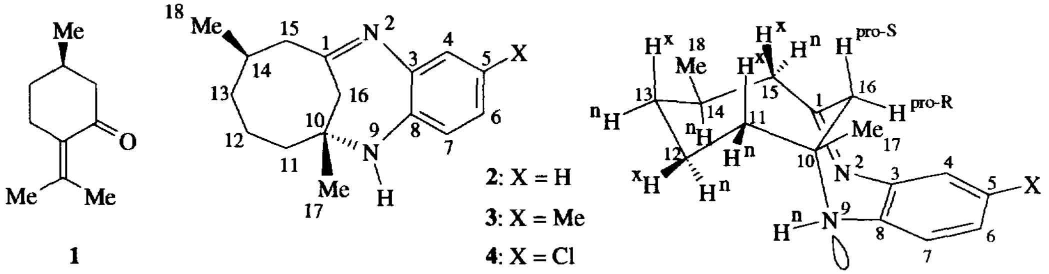
Abstract: The synthesis of the title compounds **2** - **4** from naturally occurring (*R*)-(+)-pulegone and *o*-phenylene diamines is described. Extensive NMR investigations prove that an eight-membered ring has been formed adopting a crown-type conformation.

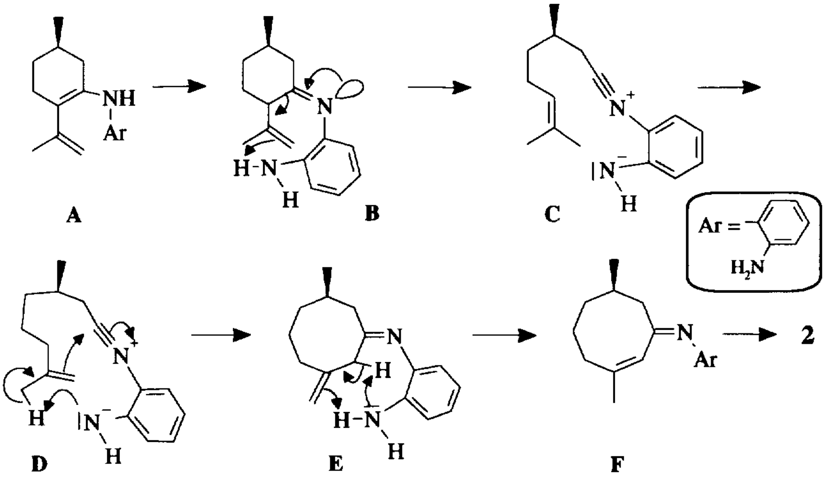
(*R*)-(+)-Pulegone (**1**) is a well-known precursor in the chiral pool and has been used for a number of chemical transformations.[1] It is a commercially available compound and a major constituent of the essential oils of *Mentha* species growing widely in the arid parts of Morocco.[2] In the course of our project to use **1** for the synthesis of enantiomerically pure compounds with potential biological activity we obtained some tricyclic benzodiazepine derivatives **2** to **4**, a class of compounds which has an effect on the central nervous system.



Scheme 1. Structures of compounds **1** to **4**

It has been shown that benzodiazepines can be produced by the condensation of enones, such as mesityl oxide, with *o*-phenylene diamines.[3] So, we tried to perform the same reaction with **1** containing an α,β-enone chromophore as well. This paper describes the first results of our experiments.

The two starting materials, **1** and *o*-phenylene diamine, were dissolved in toluene and refluxed for four days and **2** could be obtained in a yield of 68%. The reaction mechanism may be expressed as follows:



Scheme 2. Proposed Reaction Mechanism

The dieneamine **A** formed by a condensation of **1** and *o*-phenylene diamine (*via* the enimine) tautomerizes to **B** which undergoes a fragmentation to the nitrilium cation **C** (1,4-dipole). Double bond isomerization leads to **D**. This species is able to perform a 8-*exo*-digonal cyclization coupled with an allylic deprotonation to afford **E** with an eight-membered ring. The subsequent double bond isomerization to **F** with two conjugated double bonds is assisted by a pericyclic mechanism. Finally, a remarkably stereoselective intramolecular cyclization leads to **2**. The derivatives **3** or **4** can be synthesized analogously.

The structures of **2** to **4** were confirmed by establishing the connectivities of the proton and carbon atoms from the COSY experiments. In addition, COLOC signals indicating $^1H,^{13}C$ couplings *via* two or three bonds supported the constitution of the compounds. We found a consecutive sequence of CH_n-fragments (n = 1 to 3) from C-11 to C-15 and C-18. The two H-16 signals provided an AB-spin system as expected. The position of the angular methyl group C-17 was proven by a COLOC peak connecting H-17 and C-16 (three-bond coupling). The ^1H and ^{13}C signals of the aliphatic part of the molecules are remarkably similar in all three compounds proving that they have the same structure. The ^{13}C chemical shift of the imino group C-1 is $\delta = 172$ to 174 which are reasonable values. The multiplicities of the aromatic proton signals in **3** and **4** clearly showed a spin system corresponding to a 1,2,4-trisubstituted benzene. Therefore the substituent X (CH_3 or Cl, respectively) is in 5- or 6-position. An NOE-difference experiment provided the decision: irradation of the N-9 proton afforded a strong response of H-7. This signal was split into a doublet due to one *ortho*-coupling but no *meta*-coupling exists for this proton. Hence, the substituent X is in 5-position. Comparing the aromatic ^1H and ^{13}C chemical shifts of **3** and **4** with **2** afforded methyl and chlorine substituent effects which correspond excellently with those listed in textbook increment rules.[4] The C-10 configuation is *R* as proven by

NOE responses of both H-16 protons in comparable size when H-17 is irradiated. In the reversed configuration (*S*) none of the contacts is possible.

The determination of the conformation of the eight-membered ring in **2** to **4** is based on extensive NOE-difference experiments. Some signals overlapped in $CDCl_3$ so that a clear selective irradiation was not possible. In most cases, however, we were able to overcome this problem by changing solvents (acetone-d_6 and C_6D_6). Each proton signal could be irradiated selectively in at least one of these three solvents, except the two H-16 atoms. It turned out that the conformation of the eight-membered ring is close to a crown containing a double-chair (see Scheme 1). This is proven by mutual pairwise NOE contacts of H-11x, H-13x, H-15x and pro-*S*-H-16. Since pro-*R*-H-16 did not contribute to these contacts we were able assign the two H-16 protons. Moreover, there are spatial contacts between H-9, H-12n and H-14n supporting the crown conformation. Simultaneously, this is a proof that the methyl group C-18 is in quasi-equatorial position (which is consistent with the *R*-configuration of C-14) and that the NH proton can adopt the *endo*-position with the free electron pair at N-9 being *exo*.

It is interesting to note that all three mass spectra showed a very prominent fragmentation providing an [M^+-110] base peak. High-resolution mass spectra proved that the remaining ion is $C_8H_7N_2X$ (**2**: X = H; **3**: X = CH_3; **4**: X = Cl). The intensities of all other peaks are below 40%. At the moment we cannot offer a reasonable mechanism.

Experimental

NMR: Bruker AM-400 (^1H: 400.1 MHz and ^{13}C: 100.6 MHz/) and AM-300 (^1H: 300.1 MHz and ^{13}C: 75.5 MHz). Solvent: $CDCl_3$. Multipulse experiments (DEPT, NOE-difference, ^{13}C measurements with selective ^1H irradiation, HH COSY, HC COSY, COLOC) were performed using standard Bruker software.[5] IR spectra were recorded on a Nicolet 5DX instrument in KBr. Mass spectra were taken in electron-impact mode (70 eV) on Varian MAT 312 and Fisons Autospec instruments.

(10R),(14R)-10,14-dimethyl-2,9-diazatricyclo[8.5.1.0^{3,8}]hexadeca-1,3(8),4,6-tetraene (**2**)

2.00 g (13.14 mmole) of (*R*)-(+)-pulegone (**1**) and 1.42 g (13.14 mmole) of *ortho*-phenylene diamine were dissolved in 30 ml of dry toluene. Subsequently, the mixture was refluxed. Thin-layer chromatography (cyclohexane/ethyl acetate) showed that **1** had disappeared after four days. The solvent was evaporated and the residue subjected to column chromatography over silica gel (cyclohexane/ethyl acetate 7:3) producing 2.16 g of **2** (yield: 68%). M.p. 105 °C (hexane). IR (KBr): 3316, 2954, 2869, 1635, 1457, 1418, 1325, 1296, 1228, 1067, 959, 870, 810 cm^{-1}. MS (relative intensity): 242 (M^+, 27), 227 (15), 199 (28), 185 (30), 172 (16), 132 (100), 92 (9), 77 (7).

(10R),(14R)-5-Methyl-10,14-dimethyl-2,9-diazatricyclo[8.5.1.0^{3,8}]hexadeca-1,3(8),4,6-tetraene (**3**)

The same synthetic procedure as for **2** afforded **3** after 2 days. The yield was 2.36 g (70%) of **3**. M.p. 155 °C (hexane). IR (KBr): 3325, 2928, 1635, 1450, 1382, 1277, 1230, 1080, 934, 888, 761, 701 cm^{-1}. MS (relative intensity): 256 (M^+, 28), 241 (18), 213 (29), 199 (35), 186 (20), 146 (100), 107 (7), 91 (6), 78 (14), 67 (7). HRMS for the base peak: 146.0841; calculated for $C_9H_{10}N_2$ 146.0844.

(10R),(14R)-5-Chloro-10,14-dimethyl-2,9-diazatricyclo[8.5.1.0^{3,8}]hexadeca-1,3(8),4,6-tetraene (**4**)

The same synthetic procedure as for **2** afforded **4** after 3 days. The yield was 2.2 g (60%) of **4**. M.p. 142 °C (hexane). IR (KBr): 3330, 2950, 2910, 1640, 1450, 1430, 1370, 1295, 1280, 1230, 900, 735, 715 cm^{-1}. MS (relative intensity): 276/278 (M^+, 23/8), 261/263 (14/5), 233/235 (29/10), 219/221 (31/11), 206/208 (20/8), 166/168 (100/39), 131 (14), 100 (20), 67 (19). HRMS for the base peak: 166.0293; calculated for $C_8H_7ClN_2$ 166.0298.

Table 1. ^{1}H and ^{13}C Chemical Shifts of **2** - **4**[a,b]

		2		**3**		**4**	
	^{1}H signal form [c]	^{1}H [d]	^{13}C	^{1}H [e]	^{13}C	^{1}H [e]	^{13}C
1		-	171.9	-	172.6	-	173.9
3		-	141.0	-	141.7	-	142.3
4		7.09	126.7	6.95	127.1	7.12	126.6
5		6.91	121.6	-	131.7	-	126.8
6		6.91	125.2	6.56	126.0	6.92	125.2
7		6.66	122.6	6.52	122.3	6.63	123.2
8		-	137.8	-	135.3	-	136.6
10		-	69.6	-	70.2	-	70.1
11n	broad d (13.5)	1.86	36.6	1.96	36.6	1.91	36.8
11x	td (13.5,4.0)	1.14		1.20		1.22	
12n	qt (13.5,4.0)	1.42	21.3	1.50	21.6	1.48	21.6
12x	broad d (13.5)	1.66		1.73		1.73	
13n	dt (13.0,3.5)	1.62	33.9	1.69	34.2	1.69	34.1
13x	qd (13.0,3.5)	0.78		0.88		0.85	
14	m	1.57	27.7	1.61	28.0	1.59	28.1
15n	broad d (13.0)	1.90	46.2	1.98	46.4	1.95	46.4
15x	t (13.0)	0.89		0.96		0.98	
16 (pro-R)	d (12.0)	2.11	46.4	2.15	46.7	2.18	46.6
16 (pro-S)	d (12.0)	2.07		2.11		2.14	
17	s	2.27	29.9	2.34	30.2	2.34	30.2
18	d (6.5)	0.87	22.4	0.92	22.6	0.93	22.6
NH	broad s	3.4		3.6		3.6	
CH_3-Ar	s	-	-	2.28	20.6	-	-

[a] In $CDCl_3$; chemical shifts relative to solvent signals (^{1}H: $CHCl_3$, $\delta = 7.24$; ^{13}C: central peak of $CDCl_3$, $\delta = 77.0$); s ≡ singlet, d ≡ doublet, t ≡ triplet, q ≡ quartet, m ≡ multiplet.

[b] Letter "n" denotes *endo*-, letter "x" *exo*-positioned hydrogens.

[c] Aliphatic ^{1}H signal multiplicities; values in parentheses are ^{1}H,^{1}H coupling constants in Hz.

[d] All aromatic ^{1}H signals are multiplets (ABCD spin system).

[e] H-4: d (J=1.8 Hz); H-6: dd (J = 8.0, 1.8 Hz); H-7: d (J = 8.0 Hz).

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