# ON THE SYNTHESIS OF (±)-MESEMBRANONE BY THE DISSOLVING METAL REDUCTION OF 4-ARYL-4-AMINOETHYL-CYCLOHEXENONES. ISOLATION OF N-METHYL-5-(3',4'-DIMETHOXYPHENYL)-2-AZABICYCLO[3.3.1]NONAN-8-ONE

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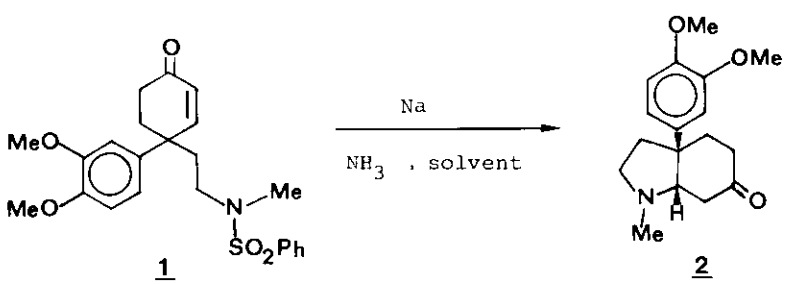
Abstract - The novel 2-azabicyclo[3.3.1]nonan-8-one derivative 4 has been isolated as byproduct in the synthesis of (±)-mesembranone (2) by the dissolving metal reduction of the 4-aryl-4-aminoethylcyclohexenone 1.

As part of our studies in the total synthesis of Sceletium (Aizoaceae) alkaloids,[1] we have recently published[2] a novel synthesis of the parent alkaloid (±)-mesembranone[3] (2) by the dissolving metal reduction of N-benzenesulfonyl 4-(3',4'-dimethoxyphenyl)-4-methylaminoethylcyclohex-2-en-1-one (1), as shown in Scheme I. We now present further observations dealing with the mechanistic aspects of this transformation.

Scheme I



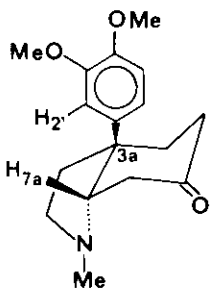

1 2

When the dissolving metal reduction of enone 1 is carried out under carefully controlled conditions at the boiling point of liquid ammonia using dry 1,2-dimethoxyethane (DME) as cosolvent, an 82% yield of 2 can be readily achieved.[2] Careful preparative layer chromatography indicated the presence of a second unknown material showing basic properties. The relevant byproduct was thus isolated in 5% yield as colorless prisms, mp 104-105°C ($Me_2CO$-hex). Elemental analysis and mass

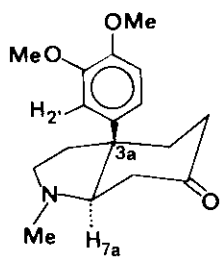
spectrometry measurements soon revealed a molecular formula $C_{17}H_{23}NO_3$ (exact molecular weight determination = 289.1676), identical to that of (±)-mesembranone[2] (2).

Interestingly enough, substitution of the DME for dry tetrahydrofuran (THF) led to a mixture of products consisting of 2 and the same byproduct in an overall 87% yield as a 5:1 mixture, respectively.

It seemed to us that if further information regarding the mechanism of the transformation depicted in Scheme I was to be forthcoming, we should fully characterize such byproduct. The possibility of having a trans-mesembrane system, such as in 3, was readily discarded upon comparison of its $^1$H-nmr data (80- and 100- MHz) with the reported[4] 60- MHz $^1$H-nmr spectrum of authentic (±)-trans-mesembranone (3). High frequency (500 MHz) Nuclear Overhauser Effect (NOE) experiments performed on the unknown sample showed no NOE between the hydrogen atom at the ring junction (i.e., the H-atom adjacent to the N-methyl grouping) and hydrogen atom(s) on the aromatic ring system, a fact that in principle suggested a trans relationship between the two substituents.




2




3

Comparative high frequency NOE experiments carried out with authentic (±)-mesembranone (2) showed the following characteristics: (a) a beautiful example of NOE between $H_{7a}$, namely the one at the ring junction, and the $H_{2'}$-aromatic hydrogen. The rotation around the $C_{3a}$-aryl bond is such that both atoms are quite close together and thus the NOE effect is strong where the aromatic signal is irradiated. The choice of the aromatic hydrogen affected is not accidental since this proton is easily isolated from the aromatic multiplet. Moreover, examination of the corresponding molecular models clearly confirms its close proximity to the $H_{7a}$-atom; (b) as expected, the reorientation time ($\tau_c$) depends on the temperature. At 297°K the spectrum shows only one NOE effect, but at 308°K the increased conformational mobility of the ring system allows for some other (weak) NOE effects to show. Selective homonuclear decoupling experiments were also carried out in order to exactly localize each H-atom of the molecule (Table I).

TABLE I. 500 MHz $^1$H-NMR Spectrum of (±)-Mesembranone (2)

| Assignment | Chemical Shift[a] (δ) ppm | Multiplicity[b] | Coupling Constants (J), Hz |
|---|---|---|---|
| $H_{2\beta}$ | 3.18 | ddd | $J_{2\beta,3\beta}$ = 8.5; $J_{2\alpha,2\beta}$ = 9.8; $J_{2\beta,3\alpha}$ = 2.8 |
| $H_{2\alpha}$ | 2.36 | q | J=9.2 |
| $H_{3\beta}$ | 2.11 | ddd | $J_{3\alpha,3\beta}$=12.9; $J_{2\alpha,3\beta}$=9.3 Hz |
| $H_{3\alpha}$ | 2.16 | ddd | $J_{3\alpha,3\beta}$=12.9; $J_{2\alpha,3\alpha}$=9.2; $J_{2\beta,3\alpha}$=2.8 |
| $H_{4\beta}$ | 2.27 | ddd | $J_{4\beta,5\alpha}$=4.8; $J_{4\beta,5\beta}$=5.4; $J_{4\alpha,4\beta}$=9.8 |
| $H_{4\alpha}$ | 2.18 | m | obscured |
| $H_{5\beta}$ | 2.44 | ddd | $J_{4\alpha,5\beta}$=9; $J_{5\alpha,5\beta}$=14.1 |
| $H_{5\alpha}$ | 2.20 | ddd | $J_{4\alpha,5\alpha}$=4.3 |
| $H_{7\alpha}$,$H_{7\beta}$ | 2.63 | d | $J_{7,7a}$=3.7 |
| $H_{7a}$ | 3.00 | t | $J_{7,7a}$=3.7 |
| N-Me | 2.35 | s | |
| 3'-OMe | 3.88 | s | |
| 4'-OMe | 3.90 | s | |
| $H_{2'}$ | 6.89 | d | $J_{2',6'}$=2.3 |
| $H_{5'}$ | 6.84 | d | $J_{5',6'}$=8.4 |
| $H_{6'}$ | 6.92 | dd | |

(a) All values refer to internal tetramethylsilane (TMS). Bruker WM-500 Spectrometer

(b) s= singlet; d= doublet; t= triplet; q= quartet; m= multiplet

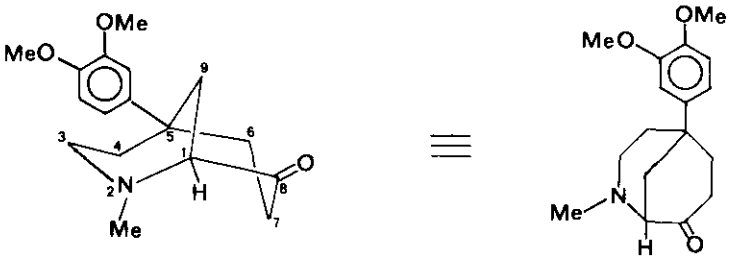
On the other hand, similar high frequency NOE experiments corroborated structure 4, N-methyl-5-(3',4'-dimethoxyphenyl)-2-azabicyclo [3.3.1]nonan-8-one, for the basic byproduct, since: (a) there is no NOE effect between the $H_{2'}$-aromatic hydrogen and that at the ring junction ($H_1$); (b) there is a strong NOE between $H_1$ and both $H_9$ (syn to the N-methyl grouping) and $H_{9'}$ (ie., the anti one). Although $H_1$ shows weak NOE interactions with other H-atoms cis to it (ie., at $C_4$ and $C_6$), molecular models show that only in structure 4 the distance between $H_1$ and $H_9$, $H_{9'}$ is indeed the shortest compared to all other cis-hydrogens. As before, selective decoupling experiments allowed assignment of all H-atoms in the molecule (Table II). Moreover, the bicyclo structure 4 allows for long range W-type[5] couplings between certain protons to show, such as $H_9$ (syn) and $H_{6\alpha}$ or $H_{9'}$ (anti) and $H_{4\alpha}$ (see Table II).

TABLE II. 500 MHz $^1$H-NMR Spectrum of 4.

| Assignment | Chemical Shift[a] ($\delta$) ppm | Multiplicity[b] | Coupling Constants (J),Hz |
|---|---|---|---|
| $H_{3\beta}$ | 2.78 | dt | $J_{3\beta,4\alpha}$=12.6; $J_{3\beta,4\beta}$=4.6; $J_{3\alpha,3\beta}$=12.6 |
| $H_{3\alpha}$ | 3.07 | ddd | $J_{3\alpha,4\alpha}$=6.7; $J_{3\alpha,4\beta}$=1.5 |
| $H_{4\beta}$ | 2.16 | m | $J_{4\alpha,4\beta}$=13.3; $J_{4\beta,6\beta}$=2.9 |
| $H_{4\alpha}$ | 2.06 | m | $J_{4\alpha,9'}$=2.4 |
| $H_{6\beta}$ | 1.99 | m | $J_{6\alpha,6\beta}$=10.9; $J_{6\beta,7\alpha}$=10.6; $J_{6\beta,7\beta}$=2.7 |
| $H_{6\alpha}$ | 2.28 | m | obscured |
| $H_{7\beta}$ | 2.22 | m | $J_{7\alpha,7\beta}$=17.6 |
| $H_{7\alpha}$ | 2.68 | m | $J_{7\alpha,7\beta}$=17.6 |
| $H_1$ | 3.24 | dt | $J_{1,7\beta}$=1; $J_{1,9}$=3.0; $J_{1,9'}$=3.0 |
| $H_9$ (syn) | 2.39 | td | $J_{9,9'}$=13; $J_{6\alpha,9}$=2.9; $J_{1,9}$=3.0 |
| $H_{9'}$ (anti) | 2.27 | td | $J_{1,9'}$=3.0; $J_{4\alpha,9'}$=2.4 |
| 3'-OMe | 3.87 | s | |
| 4'-OMe | 3.89 | s | |
| N-Me | 2.35 | s | |
| $H_{2'}$ | 6.88 | d | $J_{2',6'}$=2.0 |
| $H_{5'}$ | 6.83 | d | $J_{5',6'}$=9.1 |
| $H_{6'}$ | 6.87 | dd | |

(a) All values refer to internal tetramethylsilane (TMS). Bruker WM-500 Spectrometer.

(b) s= singlet; d= doublet; t= triplet; m= multiplet.




4

By the same token, its 25.1 MHz $^{13}$C-nmr spectrum fully supports the proposed bicyclic structure 4 (Table III). Thus, the signal at 208.3 ppm is readily assigned to a 6-membered ring carbonyl,[6] whereas the two signals at 147.2 and 148.5 ppm correspond to the ipso (ie., the methoxyl-substituted) aromatic carbon atoms. Similarly, the signal at 141.9 ppm is attributable to the $C_{1'}$-aromatic atom, while the $C_1$ atom appears as a doublet at 65.8 ppm due to the influence of the neighboring nitrogen atom and carbonyl grouping. The two protonated C-atoms at 108.4 and 110.9 are easily assigned to those benzenoid carbon atoms ortho to the methoxyls, which in turn show at 55.7 and 55.8 ppm. The N-methyl substituent is seen as a quartet in 42.9 ppm. The other ring fusion atom ($C_5$, tetrasubstituted) appears clearly at 33.6 ppm. Finally, the remaining 5 methylenes are readily assigned by comparison with the well-known[6] N-methyl piperidine and cyclohexanone systems.

TABLE III. Comparative $^{13}$C NMR Spectra of (±)-Mesembranone[7] (2) and 4[a]

| Chemical Shift / Multiplicity[b] (δ) ppm | | Assignment | |
|---|---|---|---|
| 2 | 4 | 2 | 4 |
| 35.3(t) | 33.6(s) | $C_4$ | $C_5$ |
| 36.3(t) | 36.4(t) | $C_3$ | $C_6$ |
| 39.0(t) | 37.4(t) | $C_5$ | $C_9$ |
| 40.0(q) | 38.1(t) | N-Me | $C_4$ |
| 40.6(t) | 40.8(t) | $C_7$ | $C_7$ |
| 47.8(s) | 42.9(q) | $C_{3a}$ | N-Me |
| 54.9(t) | 49.8(t) | $C_2$ | $C_3$ |
| 56.1(q) | 55.7(q) | *OMe | *OMe |
| 56.3(q) | 55.8(q) | *OMe | *OMe |
| 70.5(d) | 65.8(d) | $C_{7a}$ | $C_1$ |
| 110.8(d) | 108.4(d) | $C_{2'}$ | $C_{2'}$ |
| 111.8(d) | 110.9(d) | $C_{5'}$ | $C_{5'}$ |
| 118.3(d) | 116.4(d) | $C_{6'}$ | $C_{6'}$ |
| 140.4(s) | 141.9(s) | $C_{1'}$ | $C_{1'}$ |
| 148.0(s) | 147.2(s) | $C_{3'}$ | $C_{3'}$ |
| 149.5(s) | 148.5(s) | $C_{4'}$ | $C_{4'}$ |
| 210.8(s) | 208.3(s) | $C_6$ | $C_8$ |

(a) All values refer to internal tetramethylsilane (TMS)
(b) s= singlet; d= doublet; t= triplet; q= quartet

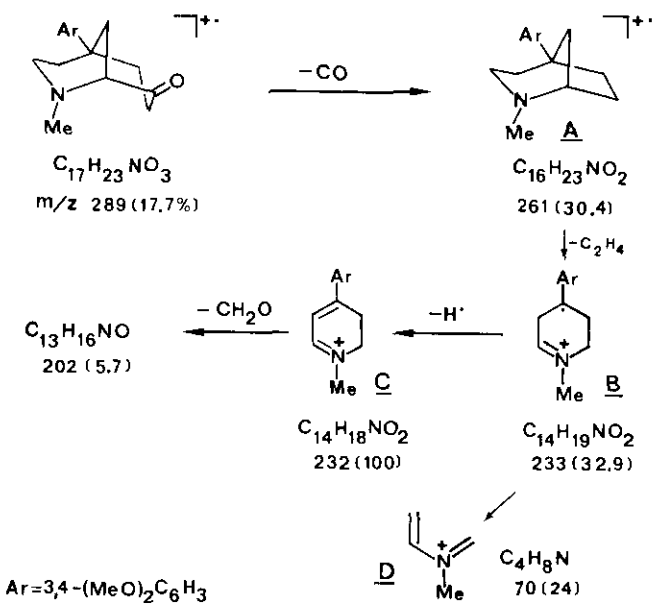
Furthermore, the mass spectrum of 4 (Table IV) supports fully the proposed bicyclic structure. The main features of the fragmentation pattern shown in Scheme II, are : (a) the absence of the significant $M^+$-1 peak which is characteristic of the mesembrane alkaloids;[8] (b) the consecutive loss of carbon monoxide (to give A, $C_{16}H_{23}NO_2$) and ethylene from the carbonyl-containing ring of 4 to generate iminium radical B ($C_{14}H_{19}NO_2$), a 6-membered nitrogenated system bearing the 3,4-dimethoxyphenyl substituent at the 4-position. Further fragmentation in a retro Diels-Alder fashion gives azadiene ion D ($C_4H_8N$). Moreover, B loses hydrogen atom to yield the base peak C ($C_{14}H_{18}NO_2$). Other fragments are indicated in Table IV.

TABLE IV. Mass Spectrum of 4.

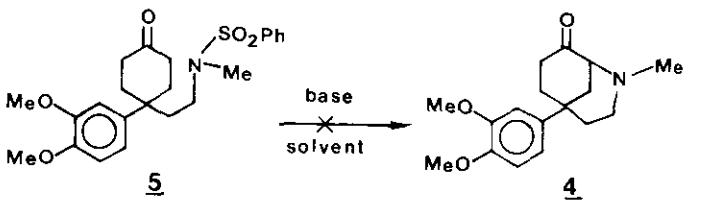
| m/z | Relative Intensity, % | Exact Mass |
|---|---|---|
| 289 | 17.7 | 289.1676 |
| 261 | 30.4 | 261.1727 |
| 233 | 32.9 | 233.1415 |
| 232 | 100.0 | 232.1336 |
| 202 | 5.7 | - |
| 109 | 9.5 | - |
| 85 | 45.6 | - |
| 83 | 41.8 | - |
| 71 | 43.0 | - |
| 70 | 24.0 | - |
| 69 | 50.0 | - |
| 57 | 74.8 | - |
| 56 | 25.3 | - |
| 55 | 50.6 | - |
| 51 | 11.4 | - |

From the mechanistic point of view, the transformation depicted in Scheme I is exceedingly interesting. In Scheme III we present a possible reaction mechanism that incorporates all of the observations recorded thus far. From an analysis of the polarographic[9] and electrochemical[10] peak potentials (*Ep*) of the two reactive functional groups present in 1, viz., a cyclohexenone and a dialkyl sulfonamide grouping,[11] one can safely assume an initial chemoselective reduction of the enone system to generate radical anion A,[12] which is rapidly trapped, intramolecularly, by the neighboring sulfonamide moiety. The resulting 6-membered cyclic intermediate B is further reduced to dianion C, which in turn can fragment in two different ways.

Scheme II

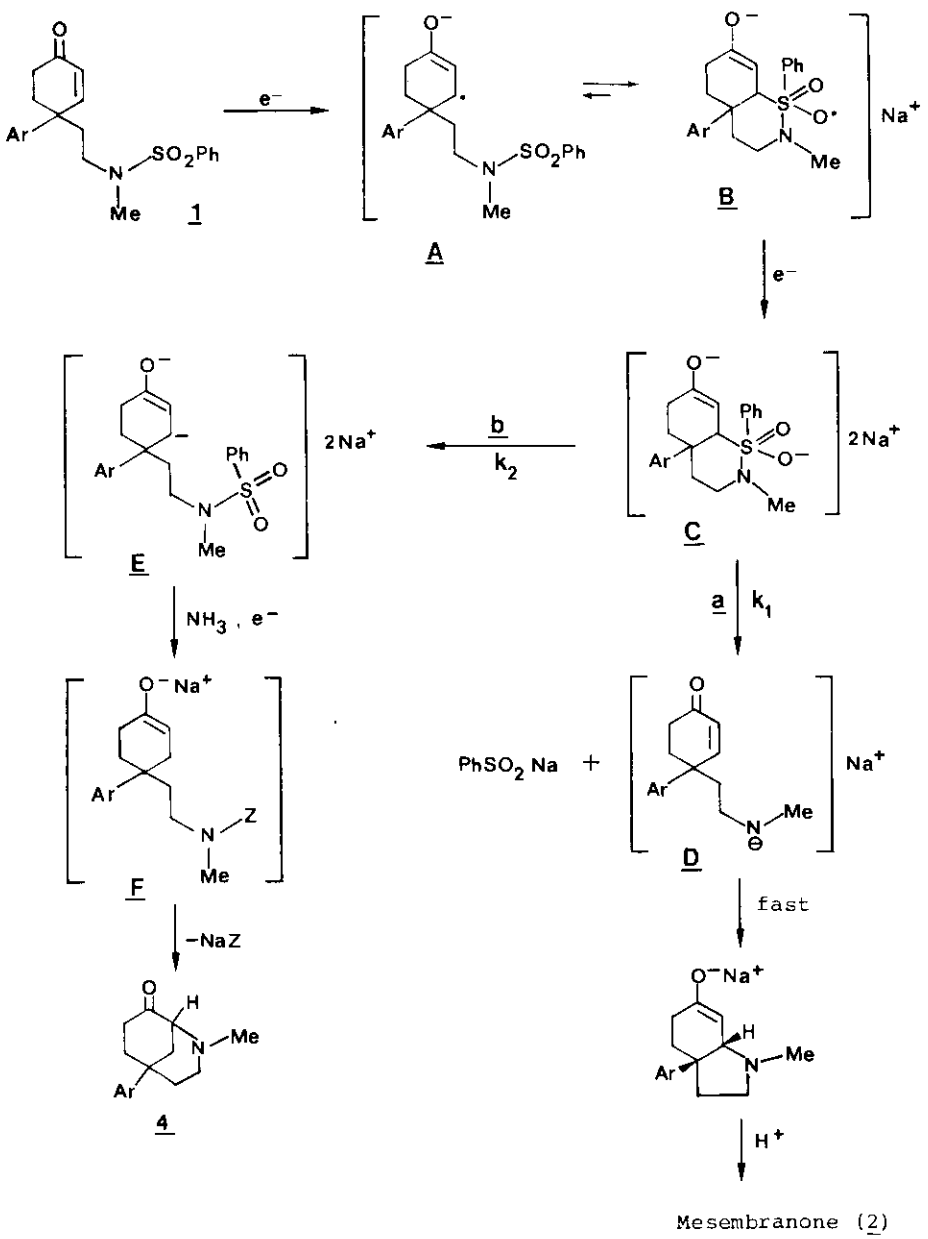



On the one hand, we postulate an irreversible enolate-assisted decomposition leading to the regeneration of the α,β-unsaturated carbonyl system and dialkyl amide ion (intermediate D), with simultaneous expulsion of sodium benzenesulfinate (Route a). Intermediate D then suffers a fast intramolecular Michael-type addition that results in the elaboration of the fully functionalized cis-mesembrane skeleton. On the other hand, intermediate C can also undergo a reversible nitrogen- or sulfoanion-assisted ring opening to dianion E, which can thus be protonated and further reduced to F. Although the exact nature of the reduced entity Z cannot be fully ascertained at this time, it should, nevertheless, present good leaving group properties, since nucleophilic attack by the enolate ion leads to formation of the bicyclic analog 4 (Route b). Moreover, an intact benzenesulfonyl grouping is not the actual leaving species as demonstrated by the fact that dihydro compound 5 fails to give any bicyclic derivatives under all possible enolate formation conditions attempted.




Finally, the solvent effects encountered during the initial experiments (vide supra) are now readily

Scheme III




Ar = 3,4-$(MeO)_2C_6H_3$

explained in terms of intermediate C (Scheme III). Namely, the use of a good metal ion chelating solvent such as 1,2-dimethoxyethane (DME) will accelerate path a (i.e., $k_1 >> k_2$) by enhancement of the electron releasing power of the "non associated" enolate. Conversely, the use of the THF will result in a more competing situation ($k_1 > k_2$) where both fragmentation pathways are co-occurring. We are presently working on the application of this methodology for the construction of complex cis-mesembrane systems such as those encountered in the fused-pyridine Sceletium alkaloids tortuosamine and alkaloid $A_4$.[3] Our complete results will be reported in due course.

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