

FUNCTIONALIZED 2-AZABICYCLO[3.3.1]NONANES. α, α' -ANNELETION OF 1-BENZYL-2,5-PIPERIDINEDIONE AND ISOLATION OF AN AZABICYCLIC ADDUCT AS STABLE HYDRATE

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Summary. The reaction of the pyrrolidine enamine derived from 1-benzyl-2,5-piperidinedione with acrolein afforded a 3,6,9-trifunctionalized 2-azabicyclo[3.3.1]nonane system, which could be isolated as a stable ketone hydrate.

The 2-azabicyclo[3.3.1]nonane (morphan) system² is present in many natural and synthetic compounds. For this reason, when functionalized, morphans have been used as intermediates in the synthesis of more complex polycyclic structures. The closure of the morphan nucleus generally implies C-1 as the pivotal atom.² In contrast, the use of the bridged C-5 as the promoter of ring closure has been little explored so far.³

We report here a new, direct entry to the 2-azabicyclo[3.3.1]nonane system consisting in an α, α' -annulation reaction from a 2,5-piperidinedione enamine by a one-pot, multistep process that implies formation of C₁-C₈ and C₅-C₆ bonds, the latter in the last step.⁴

The required enamine **2**⁵ was prepared (pyrrolidine, C₆H₆, TsOH, 3 Å molecular sieve, rfx, 45 min) in nearly quantitative yield from ketone **1**.⁶ Treatment of **2** with acrolein (dioxane, 0°C; then rt, 2 h; then H₂O, 1 h) afforded (44% yield) an epimeric mixture of pyrrolidino adducts **3a**⁷ and **3b**⁸ (approximate ratio 2:1). Although their easy epimerization precluded their separation, a sample of the major isomer **3a** could be obtained in a pure form from the corresponding hydrate **4a** (*vide infra*). The stereochemical assignment of **3a** was effected from its nmr data, in particular from the chemical shift and multiplicity of protons at the 4- and 6-positions⁷ and the shielding of C-4, as compared with **3b**, induced by a γ -effect (see Table 1).

Interestingly, a purified mixture of **3a** and **3b** partially solidified on standing. After trituration with acetone, a solid, identified as the hydrate **4a**,⁹ was obtained.¹⁰ This fact is worthy of mention since the isolation of stable ketone hydrates is unusual.¹¹ The most significant spectroscopic data of **4a** were two singlets due to the hydroxy protons in the

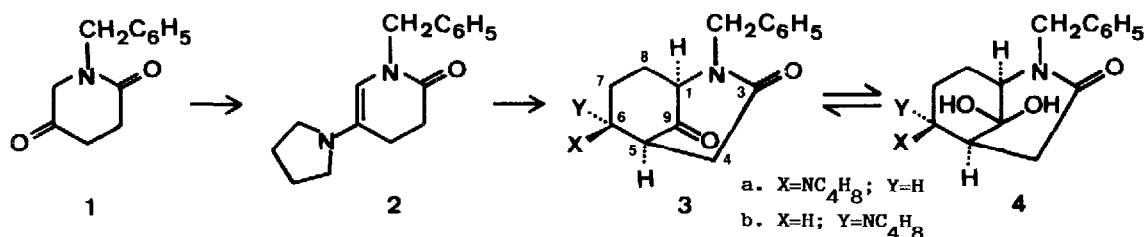


Table 1. ^{13}C -Nmr Data of Azabicyclononane Derivatives **3**^a and **4**^b

Compound	1-C	3-C	4-C	5-C	6-C	7-C	8-C	9-C	CH ₂ Ar	α -N	β -N	Ar ^c
3a	61.9	168.9	30.9	49.2	67.6	29.0	22.5	206.6	48.8	51.4	23.3	136.6
3b ^d	62.8	168.4	36.1	48.4	70.3	27.5	20.6	205.2	49.3	51.4	23.5	136.6
4a	59.7	169.9	29.6	41.3	62.1	24.2	21.4	91.9	47.9	51.1	22.8	138.3
4b ^d	60.8	170.0	34.7	38.7	65.6	21.1	18.8	92.0	48.3	51.5	22.8	138.3

a. In CDCl_3 solution; b. In $\text{DMSO}-d_6$ solution; c. Other phenyl ring carbons were found at 128.5, 128.0, and 127.2 ppm (average values, ± 0.6 ppm); d. Data from an epimeric mixture.

^1H -nmr spectrum ($\text{DMSO}-d_6$) and the chemical shift of the C-9 hydrate carbon at $\delta 91.9$ in the ^{13}C -nmr spectrum (see Table 1). The conversion of the carbonyl derivative **3a** into the hydrate **4a** is reversible since, when **4a** was heated at 110°C , it was fully reconverted to **3a**.¹² The easy hydration of the C-9 carbonyl probably occurs in order to minimize its unfavourable dipole interactions with the neighbouring amide function.

In summary, the method herein reported allows the straightforward construction of highly functionalized morphan systems.

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- ^1H -nmr (CDCl_3 , 60 MHz): 1.8 (m, 4H, CH_2), 2.50 (s, 4H, 3- and 4- CH_2), 2.3-3.1 (m, 4H, $_{-1}\text{NCH}_2$), 4.60 (s, 2H, ArCH_2), 4.80 (s, 1H, $=\text{CH}$), 7.10 (s, 5H, ArH); ir (CHCl_3): 1660, 1640 cm^{-1} .
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- 3a**: ^1H -nmr (CDCl_3 , 200 MHz): 1.55 (tq, $J = 13.5, 13.5, 4,$ and 2 Hz, 1H, 8-Hax), 1.71 (dt, $J = 13.5, 13.5, 2,$ and 2 Hz, 1H, 8-Heq), 2.63 (dd, $J = 18$ and 7.5 Hz, 1H, 4-Hax), 2.89 (m, $W_{1/2} = 15$ Hz, 1H, 6-Hax), 3.49 (d, $J = 18$ Hz, 1H, 4-Heq), 3.62 (br s, 1H, 1-H), 4.21 and 4.97 (2d, $J = 15$ Hz, 1H each, ArCH_2), 7.24-7.33 (m, 5H, ArH); ir (CHCl_3): 1740, 1640 cm^{-1} .
- 3b**: ^1H -nmr (CDCl_3 , 200 MHz): 2.55 (dd, $J = 18$ and 7.5 Hz, 1H, 4-Hax), 3.0 (d, $J = 18$ Hz, 1H, 4-Heq), 3.18 (br s, 1H, 1-H), 3.97 and 5.14 (2d, $J = 15$ Hz, 1H each, ArCH_2).
- 4a**: ^1H -nmr ($\text{DMSO}-d_6$, 200 MHz): 0.98 (qd, $J = 12.5, 12.5, 12.5,$ and 2 Hz, 1H, 7-Heq), 1.4-1.7 (m, 5H), 2.10 (m, 1H, 5-H), 2.20-2.40 (m, 6H), 3.10 (br s, 1H, 1-H), 3.31 (s, 2H, 4- CH_2), 4.13 and 4.71 (2d, $J = 15$ Hz, 1H each, ArCH_2), 5.86 and 5.89 (2s, 1H each, OH), 7.22-7.30 (m, 5H, ArH). This compound gave satisfactory elemental analysis.
- The mother liquors were found to be a mixture of ketones **3a** and **3b** and hydrates **4a** and **4b**.
- To our knowledge, the only examples recorded in the piperidine series are hydrochlorides: a) R. E. Lyle, R. E. Adel, and G. G. Lyle, *J. Org. Chem.* **1959**, *24*, 342; b) J. J. VanLuppen, J. A. Lepoivre, R. A. Dommiess, and F. C. Alderweireldt, *Org. Magn. Reson.* **1979**, *12*, 399; c) W. Wysocka, *Heterocycles* **1982**, *19*, 1.
- The ^{13}C -nmr spectrum of **4a** recorded at 60°C showed a 30% conversion into the corresponding ketone **3a**.

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