Tetrahedron Vol. 43, No. 2, pp 377 to 381, 1987
Printed in Great Britain

0040-4020/87 $5.00+.00

FUNCTIONALIZED 2-AZABICYCLO[3.3.1]NONANES. VII.[1] A NEW SYNTHESIS OF 4-AZATRICYCLO[5.2.2.$0^{4,8}$]UNDECAN-11-ONE[2]

JOSEP BONJOCH, NURIA CASAMITJANA, JOSEFINA QUIRANTE, ANTONI TORRENS, ANNA PANIELLO, and JOAN BOSCH*

Department of Organic and Pharmaceutical Chemistry, Faculty of Pharmacy, University of Barcelona, 08028-Barcelona, Spain

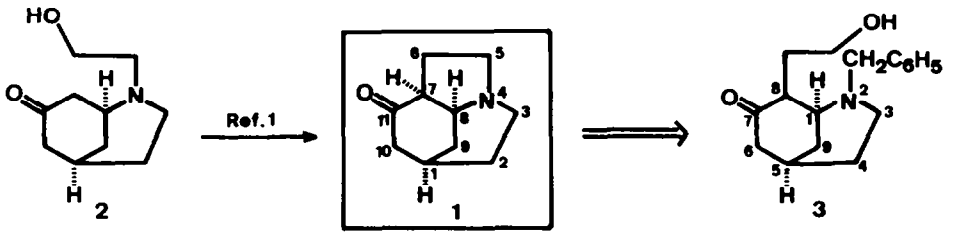
(*Received in UK* 3 *November* 1986)

Abstract—An improved method for the synthesis of 4-azatricyclo [5.2.2.$0^{4,8}$]undecan-11-one (**1**) is reported. The synthesis involves hydrogenolysis of 8-hydroxyethyl-2-azabicyclo[3.3.1]nonan-7-one **3** followed by intramolecular alkylation of the resulting secondary amine **7**. The required azabicyclic alcohol **3** was obtained by oxidative cyclization with mercuric acetate of the α-alkylated methyl 4-piperidineacetoacetate **5**.

The 2-azabicyclo[3.3.1]nonane (morphan) skeleton is found in many biologically active natural products, including *Strychnos* alkaloids as well as nonindole-containing alkaloids such as morphine. For this reason, functionalized 2-azabicyclo[3.3.1] nonanes have attracted our attention as versatile intermediates for the synthesis of more complex structures, such as pentacyclic *Strychnos* alkaloids[1] and heteroaromatic analogues of 6,7-benzomorphans.[3]

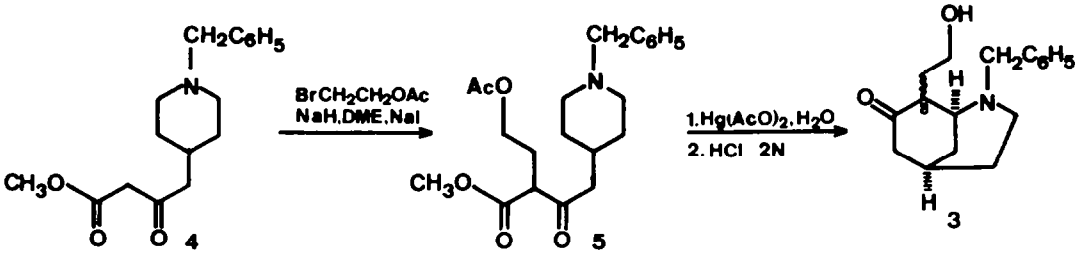
A variety of synthetic routes for constructing the 2-azabicyclo[3.3.1]nonane skeleton have been exploited so far.[4,5] In this context, we have recently developed the oxidative cyclization of 4-piperidineacetoacetates, which we have successfully applied to the synthesis of several 2-azabicyclo[3.3.1]nonan-7-ones.[1]

At present, in order to further elaborate the pentacyclic framework of *Strychnos* indole alkaloids by a methodology that implies the construction of the indolenine ring in the last synthetic step, we focus our attention to the synthesis of the 4-azatricyclo[5.2.2.$0^{4,8}$]undecan-11-one system **1**, starting from appropriate 2-azabicyclo[3.3.1]nonan-7-ones.[6,7] In a previous paper[1] we have reported the synthesis of tricyclic ketone **1** by closure of the five membered ring in the key step on treatment of the *N*-(2-hydroxyethyl)morphan **2** with mesyl chloride and further base-catalyzed cyclization. We describe here a new and shorter synthetic sequence to this ketone **1** based on the intramolecular *N*-alkylation of an appropriately 8-substituted 2-azabicyclo[3.3.1]nonan-7-one **3**.



Scheme 1

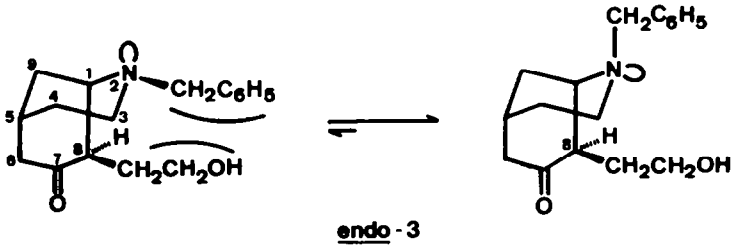
According to our synthetic plan, the required azabicyclo **3**, having a functionalized two-carbon substituent at C-8, would be prepared by our reported procedure[1] for the synthesis of 2-azabicyclo[3.3.1]nonan-7-ones, consisting in the mercuric acetate cyclization of 4-piperidineacetoacetates. However, it is worth commenting that in this case the nucleophile is a methine carbon, which constitutes a newness in this type of processes.[8] Scheme 2 outlines the two-step reaction sequence that we have successfully developed for the synthesis of **3**.



Scheme 2

Thus, the requisite α-substituted β-keto ester **5** was obtained in 63% yield by alkylation of **4** with 2-bromoethyl acetate in the presence of sodium iodide, by using sodium hydride as a base in refluxing dimethoxyethane.[11,12] Compound **5**, which gave negative the ferric chloride test, has the carbonyl form as preponderant as acyclic β-keto esters normally do. Mercuric acetate cyclization of piperidineacetoacetate **5** was effected in aqueous solution at reflux temperature. After removal the excess of the oxidizing reagent with hydrogen sulfide, the resulting cyclized β-keto ester, which was not isolated, was heated in the presence of diluted hydrochloric acid in order to induce hydrolysis of the two ester groups and decarboxylation of the resulting β-keto acid. Purification of the crude reaction mixture afforded the expected azabicyclic alcohol **3** in 20% yield.

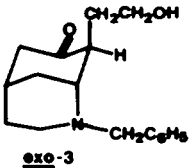
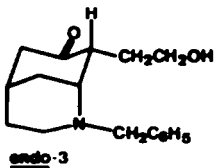
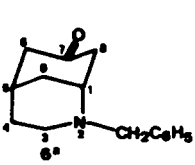
Azabicyclo **3** was isolated as an epimeric mixture, from which the major *exo* isomer was separated in a pure form. The assignment of the relative stereochemistry of the two diastereomers was made on the basis of their spectroscopic data. In the ^{13}C-NMR spectrum of *exo*-**3**, as compared with that of benzylmorphan **6** (see Table 1), the shielding of C-6 and C-9 by a γ-effect and the deshielding of C-1 and C-8 can be observed. This comparison led to the conclusion that the 2-hydroxyethyl chain located at C-8 is axial. The ^{13}C-NMR data of the minor epimer *endo*-**3** not only indicated that C-8 had the opposite relative configuration than the *exo* isomer but also a conformational change on the nitrogen atom. In this case, the *N*-benzyl group is axially oriented to relieve the steric crowding with the equatorial side chain at C-8. Accordingly, a shielding effect on C-9 and C-4 was observed as well as a strong deshielding effect on C-8. The latter can be explained by the disappearance of the γ-gauche effect exerted by the *N*-benzyl group when it was in equatorial disposition



endo-**3**

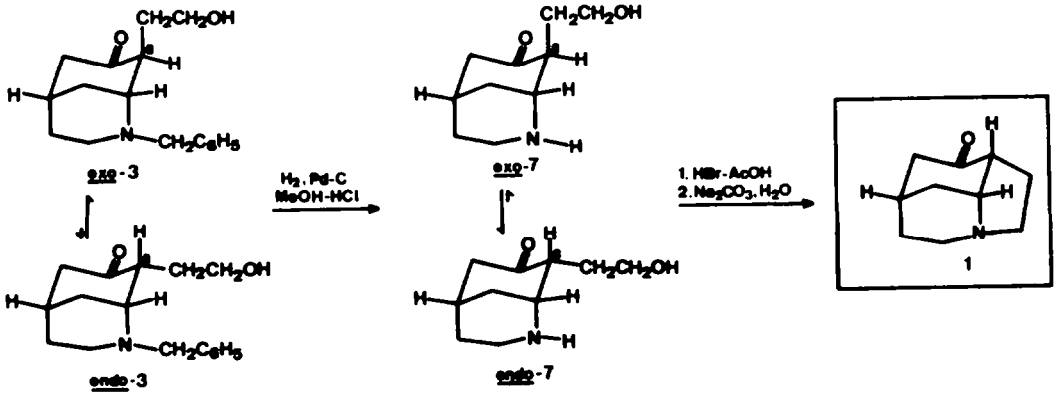
Scheme 3

Table 1. ^{13}C-NMR Data of 2-Azabicyclo[3.3.1]nonan-7-ones

	 exo-3	 endo-3	 6[a]
1-C	58.9	58.9	53.9
3-C	44.8	41.3	44.7
4-C	30.9	26.1	31.1
5-C	28.9	29.7	28.7
6-C	44.9	47.1	47.1
7-C	215.3	212.8	211.5
8-C	44.4	53.9	40.1
9-C	28.9	27.8	33.0
CH_2Ar	59.3	57.7	59.5
CH_2	34.8	30.8	--
CH_2OH	60.3	60.8	--
p-C	127.3	127.0	126.9
m-C	128.4	128.3	128.2
o-C	128.7	128.9	128.6
ipso-C	138.8	138.8	138.8

a. These assignments have been effected on the basis of the two-dimensional proton-carbon chemical shift correlation: J. Bosch, N. Casamitjana, J. Bonjoch, and M. Rubiralta, *An. Quím.* **1987**, *83C*, 000.

The next synthetic step was the debenzylation of benzylmorphan **3** by hydrogenolysis in acidic medium. This reaction was carried out from a mixture of the two epimers, in which the isomer *exo*-**3** predominated. This fact did not constitute a serious trouble[13] since carbon 8, in α-position with respect to the carbonyl group, is epimerizable. Once debenzylation was done, an epimeric mixture of the secondary β-amino ketone **7**,[14] in which the most stable *endo* isomer was preponderant, was obtained. This isomer has the C-8 substituent in equatorial disposition and, hence, is suitable for cyclization. In the ^{1}H-NMR spectrum of **7** a one-proton signal at δ3.4 attributable to the 1-H methine proton of *endo*-**7**, can be observed. The strong



Scheme 4

deshielding of this proton (Δδ+0.42 ppm) compared with that of *exo*-**3** is due to the disappearance of the shielding effect of the adjacent benzyl group as well as to the change of the axial 2-hydroxyethyl chain to an equatorial disposition.[15] Moreover, there is not any remarkable absorption in the δ≈2.8 region, where proton 8-Heq should resonate if epimerization had not occurred.

Finally, alcohol **7** was treated with hydrobromic acid in acetic acid at room temperature. The intermediate bromide was basified, whereupon spontaneous cyclization occurred[16] to give azatricyclo **1** in a 40% yield, which was identical in all aspects with that previously synthesized by another route.[1,17]

EXPERIMENTAL

General. Melting points were determined in a capillary tube on a CTP-MP 300 hot plate apparatus, and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ on a Varian XL-200 spectrometer. Chemical shifts are expressed in parts per million (δ) relative to internal TMS. IR spectra were recorded on a Perkin-Elmer 1430 spectrophotometer. Mass spectra were determined on a Hewlett-Packard 5930A mass spectrometer. Column chromatography was carried out on SiO_2 (silica gel 60, 63-200 μm, Merck) or Al_2O_3 (aluminium oxide 90, neutral, activity I, 63-200 μm, Merck). Flash column chromatography was carried out on SiO_2 (silica gel 60, 40-63 μm, Macherey-Nagel). TLC was performed on SiO_2 (silica gel 60, F_{254}, Merck) or Al_2O_3 (aluminium oxide 150, F_{254}, neutral, type I, Merck), using 70:30:5 ether-acetone-diethylamine as developing solvent, and the spots were located with UV light or iodoplatinate reagent. In oxidative cyclizations, "Hyflo Supercel" (Macherey-Nagel) was used as filtering agent. Prior to concentration, under reduced pressure, all organic extracts were dried over anhydrous Na_2SO_4 powder. Microanalyses were performed on a Carlo-Erba 1106 analyzer by Instituto de Química Bio-Orgánica, Barcelona.

Methyl α-(2-Acetoxyethyl)-1-benzyl-4-piperidineacetoacetate (**5**). A sodium hydride oil dispersion (55-60%, 4.54 g, 109 mmol) was washed under nitrogen with anhydrous hexane (3x25 ml) and anhydrous dimethoxyethane (1x25 ml). The residue was covered with dimethoxyethane (180 ml). The resulting suspension was stirred at room temperature and absolute ethanol (two drops), methyl 1-benzyl-4-piperidineacetoacetate (**4**, 27.5 g, 95 mmol), 2-bromoethyl acetate (11.5 ml, 105 mmol), and sodium iodide (7.1 g, 47.3 mmol) were sequentially added. The resulting mixture was heated at 65-75ºC for 24 h. Dimethoxyethane was evaporated and the residue was acidified with aqueous 1.2 N hydrochloric acid solution and extracted with ether. The ethereal extract was discarded and the aqueous layer was brought to pH 8 with ammonium hydroxide and extracted with chloroform. The chloroformic extracts were dried and evaporated to afford an oil which was purified by flash chromatography (SiO_2, 66:1 chloroform-diethylamine) to give the alkylated piperidineacetoacetate **5** (22.3 g, 63%) as an oil. IR ($CHCl_3$): 1735 (ester), 1710 (ketone); ^{1}H-NMR: 1.26 (m, 2H, 3-Ha and 5-Ha), 1.64 (dm, *J*=12 Hz, 2H, 3-He and 5-He), 1.8-2.0 (m, 1H, 4-Ha), 1.98 (td, *J*=12, 12, 2.4 Hz, 2H, 2-Ha and 6-Ha), 2.03 (s, 3H, $OCOCH_3$), 2.16 (q, *J*=6.5 Hz, 2H, CH_2CH), 2.44 and 2.48 (2d, *J*=11 Hz, 2H, $COCH_2$), 2.84 (dm, *J*=12 Hz, 2H, 2-He and 6-He), 3.48 (s, 2H, $ArCH_2$), 3.56 (t, *J*=7 Hz, 1H, $COCH$), 3.73 (s, 3H, OCH_3), 4.07 (t, *J*=6.5 Hz, 2H, OCH_2), 7.3 (s, 5H, ArH); ^{13}C-NMR: 22.1 (CH_3), 28.3 (CH_2CH), 32.7 (4-C), 33.3 (3-C and 5-C), 50.0 ($COCH_2$), 53.8 (OCH_3), 54.8 (2-C and 6-C), 57.3 (COCH), 63.3 ($ArCH_2$), 64.6 (OCH_2), 128.3 (*p*-C), 129.5 (*m*-C), 130.5 (*o*-C), 139.6 (*ipso*-C), 170.8 (CO ester), 204.6 (CO ketone); MS, m/e (relative intensity): 375 (M^+, 4), 256 (7), 216 (4), 188 (11), 172 (42), 159 (5), 146 (4), 120 (4), 92 (7), 91 (100), 82 (18), 65 (9), 55 (6), 43 (14). (Found: C, 67.14; H, 7.90; N, 3.97. Calcd. for $C_{21}H_{29}NO_5$: C, 67.18; H, 7.78; N, 3.73).

2-Benzyl-8-(2-hydroxyethyl)-2-azabicyclo[*3.3.1*]*nonan-7-one* (**3**). Piperidineacetoacetate **5** (3 g, 8 mmol) was added under nitrogen to a solution of mercuric acetate (26.3 g, 82 mmol) in water (210 ml) and the resulting solution was refluxed for 6h. After cooling, the reaction mixture was filtered and the residue was washed with aqueous 5% acetic acid solution (130 ml). Aqueous 20% ammonium polysulfide (32 ml) was added to the combined filtrate and washings. The resulting suspension was filtered through "Hyflo Supercel" and the precipitate was washed with water (130 ml). Concentrated hydrochloric acid (75 ml) was added to the combined filtrate and washings to obtain an approximately 2 N solution,which was refluxed for 2 h. After cooling, the solution was basified with ammonium hydroxide and extracted with chloroform. Evaporation of the dried extract give an oil which was purified by flash chromatography (SiO_2, 1:1 chloroform-ethyl acetate) to afford azabicyclic alcohol **3** as a mixture of two epimers. The epimeric mixture of **3** was further purified by flash chromatography (SiO_2, ether-carbon tetrachloride 9:1) to afford the pure *exo* epimer (170 mg, 8%) as a white solid and a nearly equimolecular mixture of *exo*- and *endo*-**3** (260 mg, 12%). *Exo*-**3** melted at 97-99ºC (ether); IR ($CHCl_3$): 3400 (OH), 1690 (CO); ^{1}H-NMR: 1.52 (dm, *J*=13 Hz, 1H, 4-He), 1.6-1.7 (m, 1H, 4-Ha), 1.7-2.0 (m, 4H, 9-H and CH_2), 2.35 (td, *J*=13, 13, 3.5 Hz, 1H, 3-Ha), 2.3-2.5 (m, 2H, 5-H and 6-He),

2.60 (dd, J=16.5 and 6.5 Hz, 1H, 6-Ha), 2.64 (qd, J =13.5, 6.5 and 1.8 Hz, 1H, 3-He), 2.96 (t, J=8.5 Hz, 1H, 8-He), 2.98 (br s, 1H, 1-He), 3.60 and 3.66 (2d, J=14 Hz, 1H each, $ArCH_2$), 3.6 (m, 2H, OCH_2), 7.1-7.4 (m, 5H, ArH); MS, m/e (relative intensity): 274 (3), 273 (M^+, 12), 172 (78), 149 (22), 91 (100), 65 (15), 55 (15), 41 (12). (Found: C, 74.88; H, 8.60; N, 5.17. Calcd. for $C_{17}H_{23}NO_2$: C, 74.70; H, 8.42; N, 5.12).

4-Azatricyclo[5.2.2.0^{4,8}]undecan-11-one(**1**). A suspension of azabicyclic alcohol **3** as a mixture of the two epimers (680 mg, 2.49 mmol) and 10% palladium on charcoal (204 mg) in methanol (10 ml) was acidified with methanolic 5 N hydrogen chloride and hydrogenated at room temperature and atmospheric pressure until total disappearance of the starting compound was observed by TLC. The catalyst was filtered off and the filtrate was evaporated to give **7**.hydrochloride. The unstable free base was obtained after the hydrochloride was treated with aqueous 10% sodium carbonate and the resulting aqueous solution was extracted with methylene chloride; ^{1}H-NMR: 1.25-2.25 (m, 6H), 2.25-2.80 (m, 6H), 3.44 (m, 1H, 1-He), 3.56-3.74 (m, 2H, OCH_2). A solution of **7**.hydrochloride (526 mg, 2.4 mmol) in 33% hydrogen bromide in acetic acid (6 ml) was stirred at room temperature for 2 h 30 min. The solution was basified with aqueous sodium carbonate solution, stirred at room temperature for 10 min, and extracted with chloroform. Evaporation of the dried extract furnished an oil which was chromatographed (Al_2O_3, 3:2 hexane-chloroform) to afford azatricyclo **1** (165 mg, 40%) identical in all respects with that previously synthesized.

Acknowledgment — This investigation was supported by the Comisión Asesora de Investigación Científica y Técnica, Spain (project number 3229/83) and, in part, by an Ajut a la Investigació de la Universitat de Barcelona.

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