Tetrahedron Letters,Vol.30,No.29,pp 3841-3844,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Maxwell Pergamon Macmillan plc

SYNTHESIS OF 2-AZABICYCLO[3.3.1]NONAN-3,7-DIONES AND THEIR FISCHER INDOLIZATION [1]

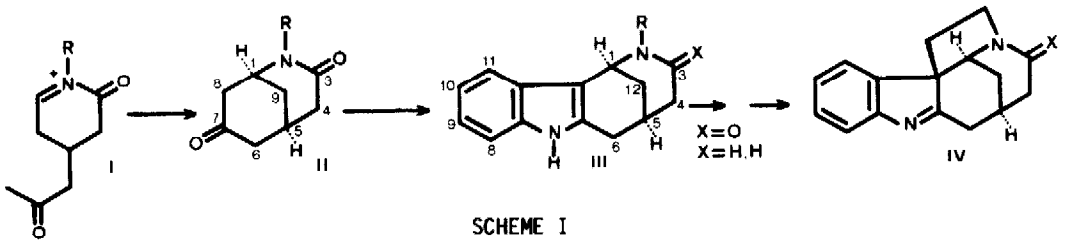
Mercedes Amat*, Enric Sanfeliu, Josep Bonjoch, and Joan Bosch*

Laboratory of Organic Chemistry, Faculty of Pharmacy,
University of Barcelona, 08028-Barcelona, Spain

Summary. A new, efficient synthetic route to functionalized morphans **6** based on the intramolecular amidoalkylation of enamides **5** and the first synthesis of 3-oxoderivatives of the hexahydro-1,5-methanoazocino[4,3-*b*]indole system are reported.

The 2-azabicyclo[3.3.1]nonane (morphan) system constitutes an essential part of many natural (*Strychnos* indole alkaloids, morphine) and synthetic (morphine-related analgesics) compounds. For this reason, when functionalized, morphans have been used as intermediates in the synthesis of more complex polycyclic structures. In previous papers we reported the synthesis of 2-azabicyclo[3.3.1]nonan-7-ones by a Mannich-type cyclization (key bond C_1-C_8) between the α-position of a ketone and an iminium salt generated either by mercuric acetate oxidation of a 4-acetonylpiperidine[2] or by acidic treatment of a 4-acetonyl-2-piperidinecarbonitrile.[3] We report here the first synthesis of 2-azabicyclo[3.3.1]nonan-3,7-diones (II),[4] by intramolecular amidoalkylation through an *N*-acyliminium ion I, in which the C_1-C_8 bond is also formed in the crucial step (Scheme I). Further elaboration of the indole nucleus should lead to tetracyclic systems of type III (X=O), having four of the five rings of pentacyclic *Strychnos* indole alkaloids.[5] Our interest in lactams III (X=O) lies in the fact that, when R is an appropriately functionalized two-carbon chain, they can allow the evaluation of the effect of the endocyclic amide carbonyl group on the cyclization upon the indole 3-position which would afford a pentacyclic *Strychnos*-type system IV (X=O).[6] Following a similar strategy from tetracyclic amines III (X=H,H), we have recently developed[6b,7] a new and general synthetic entry to pentacyclic *Strychnos* alkaloids.

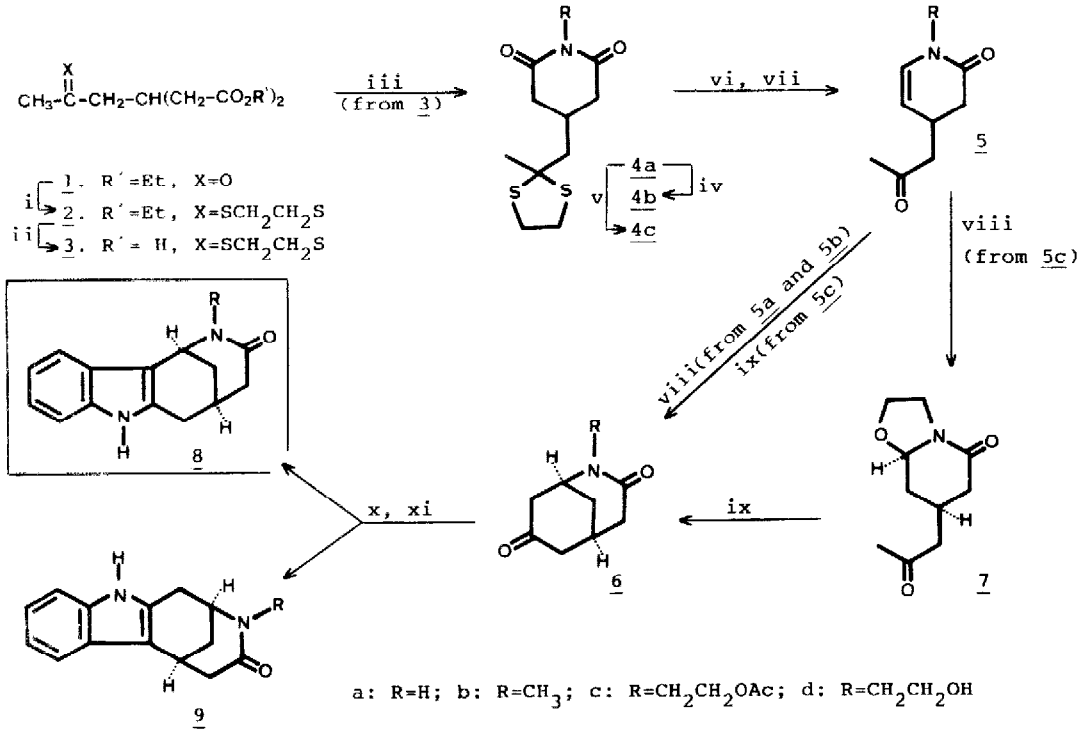
The required enamides **5** were prepared from diethyl 3-acetonylglutarate (**1**)[8] following the reaction sequence depicted in Scheme II. Acid-catalyzed $NaBH_4$ reduction of imides **4** afforded the corresponding ethoxylactams which, when treated with $HgCl_2$-HgO in order to hydrolyze the



SCHEME I

dithioacetal function, underwent simultaneous elimination of ethanol to give **5**. The intramolecular amidoalkylation[9] of **5** required strong acidic conditions. Thus, morphans **6a** and **6b** were obtained in 43% and 70% yields by stirring at room temperature a solution of **5a** and **5b**, respectively, in 9:1 $AcOH:H_2SO_4$.[10] Operating under the same conditions, enamide **5c** afforded a mixture of starting material and oxazolidine **7**, which could be converted into morphans **6c** and **6d**[11] by heating in the presence of 8:2 $AcOH:H_2SO_4$. The same result was obtained when **5c** was directly subjected to the latter conditions (60% yield). It is worth noting that, as a consequence of the mode of cyclization, the required *cis* relative configuration between the protons at the bridgehead carbons 1 and 5 is necessarily attained through this approach, without any stereochemical requisite in the starting material.

Elaboration of tetracyclic lactams III (=**8**) required the incorporation of an indole nucleus by Fischer reaction. This was accomplished by treatment of **6b** phenylhydrazone with PPA; a mixture (70% yield) of the two possible regioisomers, **8b**[12] and **9b**[13] (1:3 ratio),[14] was obtained. A similar mixture of **8c**[12] and **9c**[13] was obtained (55% yield, 1:3 ratio) when the phenylhy-



Reagents and conditions: (i) $(CH_2SH)_2$, BF_3Et_2O, 20ºC, 92%; (ii) KOH, EtOH, reflux, 95%; (iii) NH_4OH, 90-200ºC, 60%; (iv) ICH_3, NaH, DMF, 20ºC, 90%; (v) $BrCH_2CH_2OAc$, NaH, DMF, 60ºC, 90%; (vi) $NaBH_4$, EtOH/HCl, -15ºC, 93%; (vii) $HgCl_2$-HgO, CH_3OH/H_2O, reflux, 90%; (viii) 9:1 $AcOH/H_2SO_4$, 20ºC, 18 h; (ix) 8:2 $AcOH/H_2SO_4$, 60ºC, 18 h; (x) $C_6H_5NHNH_2$, EtOH, reflux, 3 h; (xi) PPA, 80ºC, 30 min.

SCHEME II

drazone of **6c** was subjected to the above reaction conditions.

Despite the fact that the hexahydro-1,5-methanoazocino[4,3-*b*]indole system (III) has received extensive attention from the synthetic standpoint[15] as a consequence of its presence in several groups of indole alkaloids (i.e. uleine type, *Strychnos*), no synthesis for 3-oxo-derivatives, such as **8**, had been reported until now.

Further studies about the usefulness of tetracyclic lactam **8c** in the synthesis of pentacyclic *Strychnos* alkaloids (closure of the five-membered E ring and introduction of the characteristic C-20[16] ethyl or ethylidene substituent)are currently in progress in our laboratory.

Table 1. ^{13}C-NMR of Compounds Containing the 2-Azabicyclo[3.3.1]nonane System[a,b]

Compound	C-1	C-3	C-4	C-5	C-6	C-7	C-8	C-9	NCH_3	NCH_2	OCH_2	CH_3CO
6a	48.9	170.6	37.1	28.7	48.3[g]	208.7	48.1[g]	29.3	--	--	--	--
6b[c]	56.1	166.8	38.1	29.7	47.8	208.4	44.8	29.7	32.5	--	--	--
6c[d]	55.6	168.0	37.9	29.3	48.1	207.5	45.0[g]	30.4	--	45.5[g]	61.7	20.7
6d[e]	55.3	168.5	36.9	28.5	48.0[g]	208.2	44.6	29.3	--	47.2[g]	59.2	--
8b	50.8	170.1	38.8	26.1	31.4[g]	132.7	112.0	30.8[g]	35.5	--	--	--
8c[d]	50.0	171.1	38.8	25.7	31.4[g]	132.8	112.1	31.1[g]	--	45.7	62.2	20.8
9b[f]	56.8	174.0	41.1	27.7	--	--	29.7	32.0	35.5	--	--	--
9c[d]	53.0	171.0	39.2	24.5	112.7	129.4	28.6	30.2	--	45.0	61.9	20.8

[a]Chemical shifts in ppm relative to TMS. Measured in $CDCl_3$ solution at 50.3 MHz unless otherwise indicated.[b]For uniformity, the numbering of the 2-azabicyclo[3.3.1]nonane ring system is used for all compounds in this table.[c]In DMSO-d_6 solution.[d]100.6 MHz.[e]In $CDCl_3$-CD_3OD solution.[f]In CD_3OD solution.[g]May be interchanged.

Acknowledgement. This work was supported by the CAICYT and the DGICYT (project numbers PB85 0260 and PB87-0062, respectively).

REFERENCES AND NOTES

1. Functionalized 2-azabicyclo[3.3.1]nonanes. Part XI. For the previous paper in this series, see: J. Bonjoch, J. Quirante, I. Serret, and J. Bosch, *Tetrahedron Lett.*, 1989, *30*, 1861.
2. a) J. Bonjoch, N. Casamitjana, and J. Bosch, *Tetrahedron*, 1982, *38*, 2883; b) J. Bonjoch, N. Casamitjana, J. Quirante, M. Rodriguez, and J. Bosch, *J. Org. Chem.*, 1987, *52*, 267; c) J. Bonjoch, N. Casamitjana, J. Quirante, A. Torrens, A. Paniello, and J. Bosch, *Tetrahedron*, 1987, *43*, 377.
3. a) J. Bonjoch, N. Casamitjana, and J. Bosch, *Tetrahedron*, 1988, *44*, 1735; b) J. Bonjoch, J. Quirante, M. Rodriguez, and J. Bosch, *Tetrahedron*, 1988, *44*, 2087.
4. For a review about the synthesis of 2-azabicyclo[3.3.1]nonanes, see: J. Bosch and J. Bonjoch, *Heterocycles*, 1980, *14*, 505. For more recent work, see reference 3a and references cited therein.
5. For a review about pentacyclic *Strychnos* indole alkaloids, see: J. Bosch and J. Bonjoch in "Studies in Natural Products Chemistry", vol. 1, Atta-ur-Rahman ed., Elsevier, Amsterdam, p. 31, 1988.
6. For the evaluation of the effect of an exocyclic amide carbonyl group, see: a) J. Bosch,

M. Amat, E. Sanfeliu, and M.A. Miranda, *Tetrahedron*, 1985, *41*, 2557; b) J. Bosch and M. Amat, *Tetrahedron Lett.*, 1985, *26*, 4951.

7. a) M. Amat, A. Linares, M.-L. Salas, M. Alvarez, and J. Bosch, *J. Chem. Soc., Chem. Commun.*, 1988, 420; b) M. Amat, A. Linares, J. Muñoz, and J. Bosch, *Tetrahedron Lett.*,1988, *29*, 6373; c) M. Amat. A. Linares, and J. Bosch, *Tetrahedron Lett.*, 1989, *30*, 000.
8. R. Lukeš and J. Paleček, *Collect. Czech. Chem. Commun.*, 1964, *29*, 1073.
9. For reviews, see: a) W. N. Speckamp and H. Hiemstra, *Tetrahedron*, 1985, *41*, 4367; b) H. Hiemstra and W. N. Speckamp, in "The Alkaloids", A. Brossi, ed., vol. 32, Academic Press, Inc., New York, 1988, Chapter 4.
10. The use of HCl/EtOH, $TiCl_4/CH_2Cl_2$, AcOH, or HCO_2H/H_3PO_4 was unsatisfactory. In some runs, cyclohexenones coming from a retro-Michael fragmentation of the initially cyclized products were detected.
11. Converted into **6c** by acetylation (AcCl, Na_2CO_3, CH_2Cl_2, 20ºC, 2 h, 90%).
12. ^{1}H-NMR **8b** (200 MHz, $CDCl_3$): 2.06 (dm, *J*=12.5 Hz, 1H, H-12); 2.24 (d, *J*=18.5 Hz, 1H, H-4); 2.33 (dm,*J*=12.5 Hz, 1H, H-12); 2.61 (d, *J*=17.0 Hz, 1H, H-6); 2.73 (m, 1H, H-5); 2.88 (dd, *J*=18.5 and 8.0 Hz, 1H, H-4); 3.08 (dd, *J*=17.0 and 5.5 Hz, 1H, H-6); 3.13 (s, 3H, NCH_3); 4.60 (br s, 1H, H-1); 7.11 (m, 2H, H-9 and H-10); 7.28 (m, 1H, H-8); 7.54 (m, 1H, H-11); 8.57 (br s, 1H, NH). **8c** (400 MHz, $CDCl_3$): 1.96 and 2.18 (2m, 2H, H-12); 2.03 (s, 3H, CH_3CO); 2.14 (d, *J*=18.5 Hz, 1H, H-6); 2.48 (d, *J*=17.0 Hz, 1H, H-4); 2.60 (m, 1H, H-5); 2.78 (dd, *J*=18.5 and 9.0 Hz, 1H, H-6); 2.93 (dd, *J*=17.0 and 5.5 Hz, 1H, H-4); 3.27 and 4.15 (2m, 2H, NCH_2); 4.22 (m, 2H, OCH_2); 4.65 (br s, 1H, H-1); 7.00 (m, 2H, H-9 and H-10); 7.17 (m, 1H, H-8); 7.45 (m, 1H, H-11); 9.0 (br s, 1H, NH).
13. ^{1}H-NMR **9b** (200 MHz, CD_3OD): 2.23 (dm, *J*=13.0 Hz, 1H, H-12); 2.35 (ddd, *J*=13.0, 4.5, and 2.5 Hz, 1H, H-12); 2.55 (dt, *J*=17.0 and 2.0 Hz, 1H, H-5); 2.80 (dd, *J*=17.0 and 5.0, 1H, H-5); 3.08 (m, 2H, H-1); 3.10, s, 3H, CH_3N); 3.51 (m, 1H, H-6); 4.16 (br s, 1H, H-2); 7.00-7.16 (m, 2H, H-8 and H-9); 7.34 (m, 1H, H-10); 7.50 (m, 1H, H-7). **9c** (400 MHz, $CDCl_3$) 2.06 (s, 3H, CH_3CO); 2.09 (m, 1H, H-12); 2.19 (m, 1H, H-12); 2.61 (d, *J*=17.0 Hz, 1H, H-5); 2.72 (dd, *J*=17.0 and 5.5 Hz, 1H, H-5); 2.85 (m, 2H, H-1); 3.03 (m, 1H, CHN); 3.41 (m, 1H, H-6); 3.92 (m, 1H, CHN); 4.03 (br s, 1H, H-2); 4.20 (m, 2H, CH_2O); 7.08 (m, 2H, H-8 and H-9); 7.26 (m, 1H, H-10); 7.42 (m, 1H, H-7); 8.42 (br s, 1H, NH).
14. When the Fischer indolization was carried out in EtOH saturated with HCl, the undesired regioisomer **9b** was obtained as the only isolable product.
15. For the synthesis of hexahydro-1,5-methanoazocino[4,3-*b*]indole systems, see J. A. Joule in "Indoles, Part 4, The Monoterpenoid Indole Alkaloids" J. E. Saxton, ed., in "The Chemistry of Heterocyclic Compounds" A. Weissberger and E. C. Taylor, eds, vol 25, John Wiley and Sons, New York, 1983, Chapter 6. For more recent work, see: a) J. Bosch, M. Rubiralta, A. Domingo, J. Bolós, A. Linares, C. Minguillón, M. Amat, and J. Bonjoch, *J. Org. Chem.*, 1985, *50*, 1516; see also reference 3b and references cited therein.
16. Biogenetic numbering corresponding to the C-4 position of III.

(Received in UK 6 June 1989)