Tetrahedron Letters, Vol.31, No.17, pp 2449-2452, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

THE FISCHER INDOLIZATION OF 2-AZABICYCLO[3.3.1]NONAN-7-ONES. A NEW ENTRY TO THE DASYCARPIDAN RING SYSTEM[1]

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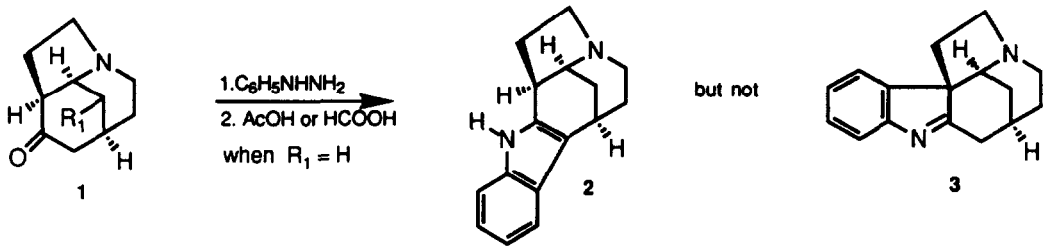
Abstract: The regioselectivity of the Fischer indole synthesis from 2-azabicyclo[3.3.1]nonan-7-ones **4b-d** using three different acid catalysts is studied, an ethyl substituent at the 9-position promoting indolization upon the C-8 carbon.

A common strategy for the synthesis of indole alkaloids consists in the use of non-indolic starting materials, with construction of the indole ring in a late synthetic stage from azapolycyclic intermediates having the appropriate functionality and stereochemistry. In this context, the Fischer indolization[2] has constituted a useful tool[3] despite the fact that the control of the regioselectivity of this reaction is difficult as a variety of factors can determine the regiochemistry of the process.

Recently, we have reported[4] that the Fischer indolization from the tricyclic ketone **1** (R_1=H), which has rings CDE of *Strychnos* indole alkaloids,[5] leads to the unnatural regioisomer **2** coming from cyclization upon the methylene carbon. The desired indolenine **3**, having the pentacyclic ring system of *Strychnos* alkaloids was not detected (Scheme 1). The greater stability of the intermediate enehydrazine that leads to the indole **2**, as compared with that of the bridgehead double bond isomer required for the cyclization to **3**, could account for this result.[6]

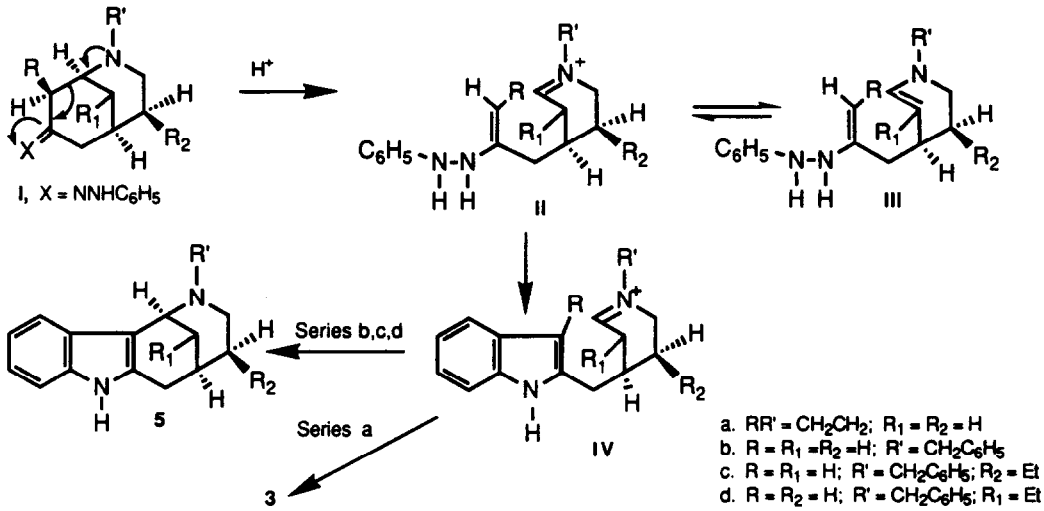
In fact, we felt that hydrazone **IIa**, derived from the tricyclic β-amino ketone **1** (R_1=H), would lead, at least to some extent, to the desired *Strychnos*-type indolenine **3** through an alternative mechanism (Scheme 2) involving an initial ring-opening by way of a retro-Mannich type fragmentation,[7] further regioselective Fischer indolization of the generated enehydrazine **IIa**, and finally cyclization[8] of the resulting stemmadenine-type intermediate **IVa**.



Scheme 1

It does not seem unreasonable to assume that the presence of an ethyl substituent at the bridge carbon (R_1 = Et; the same position as in the pentacyclic *Strychnos* alkaloids having the Aspidospermatan skeleton)

increases the stability of the enamine **III**,[9] which is in equilibrium with the iminium cation **II**, thus favoring the operation of this hypothetical mechanism.



Scheme 2

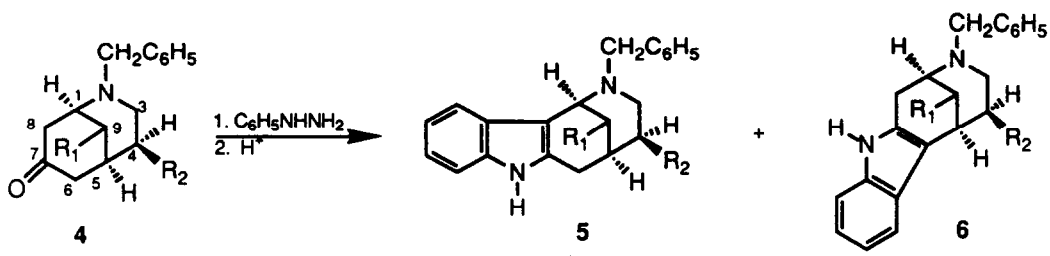
In order to assess the effect of this ethyl substituent on the regioselectivity of the Fischer indolization, we decided to study this reaction from the related, more accessible bicyclic ketones **4b**[10] (lacking the substituent), **4c**[1] (Strychnan-type; in which the substituent is at the 4-position), and **4d**[1] (Aspidospermatan-type; having the ethyl substituent at the bridge carbon).

The results, using three different acid catalysts, are summarized in Scheme 3 and Table 1. In all series, mixtures of the tetracyclic *Strychnos*-type systems **5**[11] and the unnatural regioisomers **6**[12] were obtained. However, significantly, only in the Aspidospermatan series (series **d**) the yield of the *Strychnos*-type regioisomer was higher than the yield of the unnatural one, irrespectively of the acid catalyst used. Furthermore, it is worth commenting upon the formation of **5d** as the only product when the indolization was promoted by acetic acid.

Taking into account the structural similarity of β-amino ketones **4b-d**, the observed regioselectivity in the Fischer indolization of **4d** can be indicative of the operation, to some extent in this case, of the mechanism depicted in Scheme 2 and, consequently, of the favorable effect upon the regioselectivity exerted by the ethyl substituent[13] located at the bridge carbon of the morphan nucleus.

It is well known that, when the Fischer indolization is performed at low acidities, the product coming from the most stable enehydrazine is preferentially formed.[15] According to this fact, the different result of the indolization with AcOH in series **b** and **c** could simply reflect the different stability of the intermediate enehydrazines: in the series **c**, due to the presence of an equatorial C-4 ethyl substituent, the enehydrazine that possesses a C_6-C_7 double bond would have less steric interactions than the C_7-C_8 double bond regioisomer (see Dreiding stereomodels).

Scheme 3 and Table 1. Fischer Indolization of 2-Azabicyclo[3.3.1]nonan-7-ones 4b-d



Starting Ketone	Acid[a]		Product (Yield)[b]	
	i	13	.....	9
Series **b**	ii	--[c]	.....	40[d]
(R_1=R_2=H)	iii	12[e]	.....	18[e]
	i	--	.....	20
Series **c**	ii	--.	.....	57
(R_1=H; R_2=Et)	iii	14	.....	20
	i	26	.....	--
Series **d**	ii	30	.....	15
(R_1=Et; R_2=H)	iii	17	.....	10

(a) i : AcOH, 100°C, 50 min; ii : HCl-EtOH (2.5 N), rfx, 3 h; iii : PPA, 95°C, 30 min. (b) Reported yields are for purified materials isolated by column chromatography. (c) Trace by TLC. (d) A similar regioselectivity was observed from the *N*-methyl analogue: reference 10. (e) A similar regioselectivity was observed from *N*-alkyl-2-azabicyclo[3.3.1]nonan-3,7-diones: reference 16.

From a synthetic standpoint, the Fischer indolization of **4d** establishes a new entry to tetracyclic dasycarpidan-type compounds. Tetracycle **5d** can be considered a synthetic precursor of both the alkaloids of the uleine group and the pentacyclic *Strychnos* alkaloids having the Aspidospermatan skeleton. The synthesis of the tricyclic ketone **1** (R_1 = Et) is in progress in our laboratory.

Acknowledgment. Support for this research was provided by the DGICYT (Spain) and by the CIRIT (Catalonia) through Grants PB 88-0316 and AR-88-100, respectively. Thanks are also due to the Departament d'Ensenyament (Generalitat de Catalunya) for a fellowship given to one of us (J.G.).

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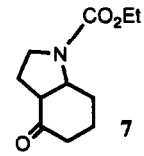
6. The formation of the two possible regioisomers (indole and indolenine) by Fischer indolization of **7**, a bicyclic amino ketone lacking the ethano bridge that performs the piperidine ring of **1**, is in accordance with this interpretation: Fritz, H.; Rubach, G. *Liebigs Ann. Chem.* **1968**, *715*, 135.



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7. A similar ring opening occurs in 9-ethyl-2-azabicyclo[3.3.1]nonan-7-ones: see reference 1.

8. For similar cyclizations in the context of the synthesis of *Strychnos* alkaloids, see: (a) Schumann,D.; Schmid, H. *Helv. Chim. Acta* **1963**, *46*, 1996; (b) Harley-Mason, J. *Pure Appl. Chem.* **1975**, *41*, 167 and references cited therein.

9. For an example in which the presence of an alkyl substituent at the 3-position of a 1,4,5,6-tetrahydropyridine increases the stability of the enamine, see: Grierson, D. S.; Vuilhorgne, M.; Husson, H.-P.; Lemoine, G. *J. Org. Chem.* **1982**, *47*, 4439.

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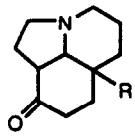
11. Identified by comparison with samples previously obtained by alternative procedures. **5b**: Bosch, J.; Bonjoch, J.; Diez, A.; Linares, A.; Moral, M.; Rubiralta, M.*Tetrahedron* **1985**, *41*, 1753; **5c**: Amat, M.; Linares, A.; Salas, M.-L.; Alvarez, M.; Bosch, J. *J.Chem. Soc. Chem. Commun.* **1988**, 240; Bonjoch, J.; Quirante, J.; Linares, A.; Bosch,J. *Heterocycles* **1988**, *27*, 2883; **5d**: Bonjoch, J.; Casamitjana, N.; Gràcia, J.; Bosch, J.*Tetrahedron Lett.* **1989**, *30*, 5659.

12. Satisfactory spectroscopic data were obtained for each reaction product. ^{1}H-NMR (200 MHz, $CDCl_3$): **6b**: 1.58 (dm, J= 12 Hz, 1H, 5-Heq) 1.83 (dq, J = 12 and 3 Hz, 1H, 12-H_R), 2.04 (tt, J = 12 and 3 Hz, 1H, 5-Hax), 2.20 (dtJ = 12 and 3 Hz, 1H, 12-H_S), 2.29 (td, J = 12 and 3 Hz, 1H, 4-Hax), 2.52 (dm, J = 12 Hz, 1H, 4-Heq), 2.67 (dd, J = 18 and 6 Hz,1H, 1-Hax), 3.10 (d, J = 18 Hz, 1H, 1-Heq), 3.36 (m, 2H, 2- and 6-H), 3.70 (s, 2H, NCH_2Ar), 7.1-7.4 (m, 10H, ArH). **6c**: 0.92 (t, J = 7 Hz, 3H, CH_3), 1.30 (m, 2H, CH_2CH_3), 1.81 (dt, J = 12 and 3Hz, 1H, 12-H_R), 1.94-1.98 (m, 2H, 4- and 5-Hax), 2.16 (dt, J= 12 and 3 Hz, 1H, 12-H_S), 2.54 (d, J = 8 Hz, 1H, 4-Heq), 2.59 (dd, J = 18 and 6 Hz, 1H, 1-Hax), 3.06 (d, J = 18 Hz, 1H, 1-Heq), 3.24 (m, 1H, 6-H), 3.34 (m, 1H, 2-H), 3.66 and 3.73 (2d, J = 13 Hz, 1H each, NCH_2Ar), 7.05-7.45 (m, 9H, ArH), 7.9 (br, 1H, NH). **6d**: 0.88 (t, J = 7.5 Hz, 3H, CH_3), 1.22 (qn, J = 7.5 Hz, 2H, CH_2CH_3), 1.6 (m, 1H, 5-Heq), 1.9-2.1 (m, 2H, 5-Hax and 12-H), 2.20 (td, J =12 and 3 Hz, 1H, 4-Hax), 2.47 (dm, J = 12 Hz, 4-Heq), 2.56 (dd, J = 18 and 6 Hz, 1H, 1-Hax), 3.00 (d, J = 18 Hz, 1H, 1-Heq), 3.19 (m, 1H, 2-H), 3.28 (m, 1H, 6-H), 3.63 and 3.75 (2d, J = 13 Hz, 1H each, NCH_2Ar), 7.1-7.4 (m, 9H, ArH), 7.8 (br, 1H, NH).

13. The Fischer indolization of the tricyclic β-amino ketones **8a**[14a] and **8b**[14b] has also been reported to occur with different regioselectivity, the ethyl substituent promoting indolization upon the methine carbon.



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a. R = H
b. R = Et

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(Received in UK 16 February 1990)