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Azabicyclo[3.2.1]octene derivatives obtained by rearrangement reactions in course of the catharanthine synthesis

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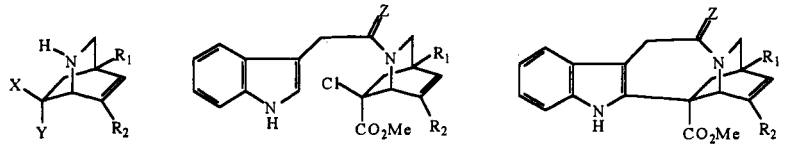
Abstract In the course of our synthesis of the alkaloid catharanthine **1a** (**2→4→6→1**)[2,3], allocatharanthine **1b** and deethylcatharanthine **1c**, several azabicyclo [3.2.1]octene derivatives were obtained by rearrangement of the isoquinuclidine ring system. The structures and stereochemistry of the azabicyclo[3.2.1]octene derivatives were determined by various NMR methods (NOE and two-dimensonal INEPT experiments).

On coupling of the alkaloid catharantine **1a** with vindoline antitumor vinblastine derivatives can be obtained[1].

The main synthetic route[2,3] of **1** (**2→4→6→1**) (**Figure 1**) was accompanied by rearrangement reactions of the azabicyclo[2.2.2]octene skeleton[4]. To avoid the unwanted rearrangement we .tried to protect the nitrogen of the isoquinuclidine by acylation. Starting from **2** a simple acylation with indolyl-acetic acid pivalic acid mixed anhydride (DMF, rt.) took place in good yield. On the other hand derivative **3** having the chlorine atom in endo position proved to be unstable under similar conditions.

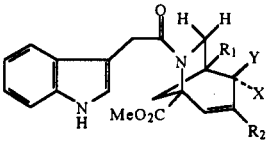


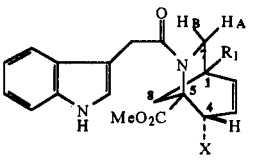
2 X=Cl, Y=CO_2Me **4** Z=O (a) R_1=H, R_2=Et **1** Z=H_2
3 X=CO_2Me, Y=Cl **5** Z=H_2 (b) R_1=Et, R_2=H **6** Z=O
(c) R_1=R_2=H

Figure 1

Starting from **3c** several 6-azabicyclo[3.2.1]octenes were obtained .(**3c**→ **7+8+10+15+16**). In addition to the earlier reported products **7** and **8**[2,3], when using another eluant for column chromatography separation, we isolated some by-products **10, 15** and **16** in low yield. Mangeney and Langlois observed the rearrangement of the catharanthinic acid resulting in 6-azabicyclo[3.2.1]oct-2-ene derivative[5]. In the course of the mechanistic study of the above reaction they proposed an intermediate with 6-azabicyclo[3.2.1]oct-3-ene skeleton. In our case we could isolate both types of rearranged derivatives confirming their suggestion.The above mentioned acylation reaction of the isoquinuclidines containing ethyl group (**3a** and **3b**) led to the corresponding 6-azabicyclo[3.2.1]oct-3-enes (**3a**→**13+14**; **3b**→**11+12**).

Compound **18** (**type A**) was prepared by irradiation of the mixture of **7** and **8** (**type B**) in methanolic solution.





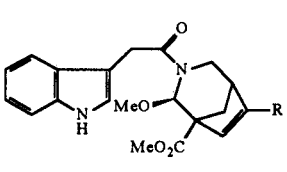
type B **7** R_1=Y=R_2=H, X=Cl
8 R_1=Y=R_2=H, X=Br
9 R_1=Y=R_2=H, X=OH
10 R_1=X=R_2=H, Y=Cl
11 Y=R_2=H, X=Cl, R_1=Et
12 X=R_2=H, Y=Cl, R_1=Et
13 Y=R_1=H, X=Cl, R_2=Et
14 Y=R_1=H, X=Br, R_2=Et

type A **15** R_1=H, X=Cl
16 R_1=H, X=Br
17 R_1=Et, X=OMe
18 R_1=H, X=OMe

Figure 2

The most important step of our synthesis was the ring closure reaction between the indole C-2 and isoquinuclidine C-7 positions. On heating **4c** in nitromethane with $AgBF_4$, rearranged ring closed products were obtained[6].

Irradiation of **4a,b,c** led in all three cases to 5-oxo-catharanthine and its derivatives **6a,b,c** and other type of products **19a,b,c** respectively[2,3].



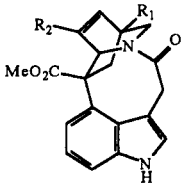


Figure 3 **20** R=H, **21** R=Et (**type C**) **19**

Depending on the position of the ethyl substituent and the reaction conditions three different types of rearranged products were obtained (**Figure 3**). Irradiation of the deethyl derivative **4c** and the 6-ethyl compound **4a** in methanolic solution resulted in 3-indolyl-acetyl-3-azabicyclo[3.2.1]oct-6-ene derivatives **20** and **21** (**type C**) containing methoxy group instead of chlorine atom[2,3]. Surprisingly, when **4c** was irradiated in THF/water a byproduct **9** (**type B**) could be observed[2]. Irradiating the 4-ethyl derivative **4b** the obtained byproduct **17** possessed a 6-azabicyclo[3.2.1]oct-2-ene skeleton (**type A**) unlike in the case of the deethyl- and 6-ethyl-derivatives.

The application of NMR methods (HETCOR, COSY, INAPT, 2D INEPT, NOE) helped us to distinguish between the structures with different ring sizes. The abundance of various derivatives with 6-azabicyclo-[3.2.1]octene skeleton, differing in the type and stereochemistry of the substituents prompted us to study the effect of stereochemical factors and substituents on the vicinal and geminal ^{13}C-^{1}H coupling constants[7].

Distinction between structures A (**15-18**) and B (**7-14**) was made by applying long-range hetero-correlation and NOE difference methods. Since the relative orientation of the C2- (**type B**) or C4- (**type A**) substituents did not follow from the homonuclear couplings of the H2 or H4 protons, the stereo-chemistry was determined by NOE experiments. Thus for the **type B** molecules irradiation of H2α in **10** and **12** gave NOE response on the H8α proton, while in the C2α substituted cases (**7-9**, **11**, **13**, **14**) NOE enhancement was observed between the H2β and $H7_A$ protons. By contrast, only one stereoisomer was found for the **type A** compounds (**15-18**). Upon irradiation of the H4 resonance no NOE effect was found on H8α, which is consistent with the α orientation of the C4 substituents in all **type A** compounds.

The Karplus-type dihedral angle dependence of the $^{3}J(C,H)$ coupling values, inferred from selective 2D INEPT experiments, corroborated the above stereochemistry. Examination of the Dreiding models suggests that the C8 and H4 β atoms have about the same - nearly planar - stereo-arrangement in the **type A** molecules as the C8 and H2β atoms in the **type B** molecules. The $^{3}J(C8,H4)$ couplings (2.8-3.2 Hz) correlate well with $^{3}J(C8,H2\beta)$ values (3.0-4.2 Hz), while the $^{3}J(C8,H2\alpha)$ values (0.8-1.0 Hz) reflect the ~ 90° dihedral angle between the pertinent atoms. However, it should be noted, that the electronegative substituent in position c of the $^{13}C_a$-C_b-C_c-^{1}H coupling path decreases the $^{3}J(C8,H2)$ couplings in comparison with the $^{3}J(H8\alpha,C7)$ and $^{3}J(H8\beta,C7)$ coupling pairs, where similar steric dependence was also found (see e.g. compound **18** in the **Table** and **Figure 4**).

It seems interesting to compare the vicinal carbon-proton couplings of compounds **6a**, **19c** and **18**, having the same structural units (**Figure 4**) in different ring sizes.

Inspection of the Dreiding models revealed that the steric arrangement of the protons and carbons is practically the same for the 6+6-membered rings in **6a** and **19c**, which is well reflected by their similar vicinal ^{1}H-^{1}H and ^{13}C-^{1}H couplings (see **Table**). By contrast, in the 6-azabicyclo[3.2.1]octenes one of the rings is five-membered, which implies the alteration of the bond-angles between coupled protons and carbons. These changes are best seen on the coupling of the H_b proton, and C_c carbon (see **Table).**

Table: Homo- and heteronuclear coupling values (Hz)

	H_b,$H_{a\beta}$	H_b,$H_{a\alpha}$	H_b,H_{cA}	H_b,H_{cB}	C_c,$H_{a\beta}$	C_c,$H_{a\alpha}$	C_b,$H_{a\beta}$	C_b,$H_{a\alpha}$	C_d,$H_{a\beta}$	C_d,$H_{a\alpha}$
6a	1.8	4.0	2.0	3.0	3.4	8.0	3.5	2.8	7.8	1.5
19c	1.5	4.0	2.0	2.5	4.1	7.4	3.7	3.0	8.1	1.5
18	3.8	0.8	0.5	4.0	<0.5	7.2	3.4	1.5	7.4	1.4

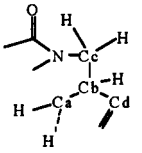


Figure 4

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