

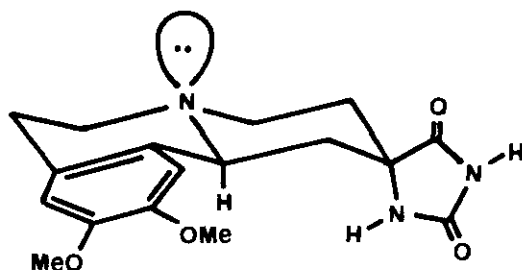
STEREOCHEMISTRY OF DIASTEREOMERIC 9,10-DIMETHOXY-1,3,4,6,7,11b-HEXAHYDROSPIRO[BENZO-[a]QUINOLIZIN-2,5'-IMIDAZOLIDINE]-2',4'-DIONES

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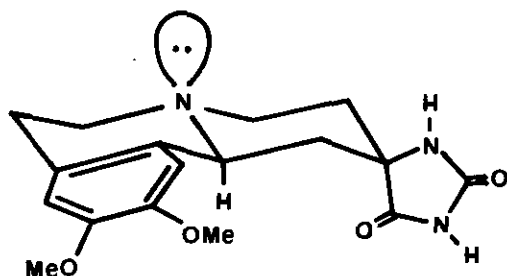
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Abstract — The structures of the two diastereomeric title compounds obtained by the Bucherer-Bergs and Read procedures are respectively assigned to α and β isomers on the basis of ^1H -nmr, ^{13}C -nmr and chemical reactivity data. Both compounds present a predominant *trans* conformation as shown by ir, ^1H -nmr and ^{13}C -nmr data.

The interesting biological activities shown by many 2-substituted benzo[a]quinolizidines¹⁻⁵ induced us to study the 2-spiro derivatives of the mentioned ring system. The preparation of 2-spirohydantoins can be achieved by application of Bucherer-Bergs⁶ and Read⁷ procedures to 9,10-dimethoxybenzo[a]quinolizidin-2-one, yielding two possible diastereomeric spiro compounds (α and β). Since some benzo[a]quinolizidines present stereospecificity in their pharmacological action^{1,2}, we considered of interest the elucidation of the stereochemistry of these diastereomers. Mechanistic studies carried out by Edward and Jitransgri⁸ show that the Bucherer-Bergs reaction of substituted cyclohexanones yields as main product the α isomer with the 4'-carbonyl function of the spirohydantoin ring in the less sterically hindered position, while the Read reaction yields as the major product the β isomer with this carbonyl group in the sterically more hindered position. Assuming the same orientation to take place in the case of 9,10-dimethoxybenzo[a]quinolizidin-2-one and the system to adopt a *trans* conformation, the structures of both diastereomers would be the following :



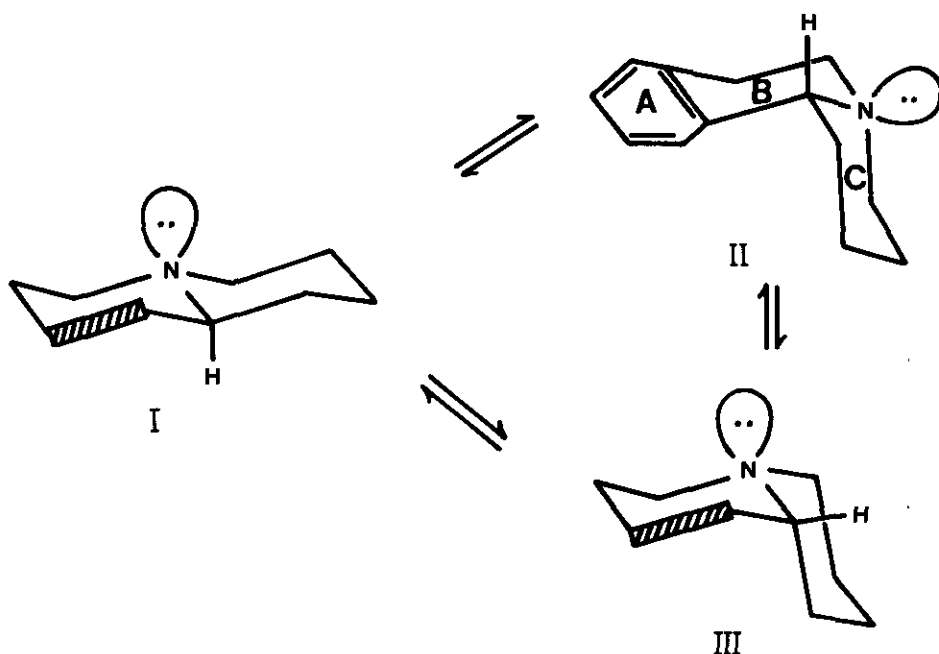
A
Bucherer- Bergs product
 α isomer



B
Read product
 β isomer

The present work shows the applicability of Edward and Jittransgri's rule⁸ by determining the configurations of the isomeric spirohydantoins obtained from 9,10-dimethoxybenzo[a]quinolizidin-2-one⁹; the preparation of these hydantoins will be reported elsewhere together with some of their pharmacological properties.

It is well known that the benzo[a]quinolizidine nucleus may exist as an equilibrium mixture of one B/C *trans* quinolizidine (I) and two B/C *cis* quinolizidine systems (II and III) (Scheme 1). Although the configuration of the nitrogen atom in structure I is opposite to that in II and III, the three systems are usually considered as conformers.



Scheme 1

The different conformers of benzo[a]quinolizidine have already been well characterized by a variety of ir^{10,13}, ¹H-nmr¹¹ and ¹³C-nmr¹²⁻¹⁵ methods. The appearance of Bohlmann bands at ca. 2750 cm⁻¹ (assigned to ν C α -H of C₄ and C_{11b}) and at ca. 2800 cm⁻¹ (assigned to ν C α -H of C₆) is indicative of a *trans* quinolizidine conformation¹³. Consequently, the observed values (Table 1) suggest a main contribution of *trans* conformer for both 2-spirohydantoin isomers A and B.

Table 1 : Main features of ir and 200 MHz ¹H-nmr spectra of compounds A and B

Spectral band	Compound A	Compound B
Ir (KBr) Bohlmann bands	2755 (m), 2795 (w)	2755 (m), 2800 (w)
¹ H-nmr (d ₅ -pyridine)		
N ₃ -H	12.45 (broad s)	12.35 (broad s)
N ₁ -H	9.96 (s)	9.38 (s)
Ar-H	6.91, 6.71 (2 s)	6.96, 6.67 (2 s)
C _{11b} -H	3.75 (m)	4.41 (broad d, J=10 Hz)
C ₄ ax-H		3.37 (m)
OMe	3.77, 3.71 (2 s)	3.71, 3.69 (2 s)

¹³C-nmr can be considered as the most reliable spectroscopic tool for conformational studies of benzo[a]quinolizidine systems. Table 2 shows the assignments made for the ¹³C-nmr spectra of compounds A and B. The techniques used for the assignment are : multiplicity of signals by proton coupling, long-range couplings and literature results.

The partial delocalization of the nitrogen lone pair electrons into the antiparallel C-H bond affects the coupling constant¹⁶. As a result, the ¹J (¹³C-H) for a *cis* conformation of the proton and the nitrogen lone pair is 6-12 Hz larger than that for the *trans* orientation. Van Binst and Tourwé reported¹² a coupling constant in the range of 126-133 Hz for several *trans* benzo[a]quinolizidines while the *cis* conformers have coupling constants of 139-143 Hz. C_{11b} shows ¹J (¹³C-H) values of 130 and 131 Hz for compounds A and B, respectively, which clearly points to a *trans* conformation for both compounds¹⁷.

This conclusion is confirmed by the chemical shifts for C₆ and C₇. The observed values for C₆ (52.60 and 51.98 ppm) and C₇ (29.85 and 29.89 ppm) in compounds A and B respectively are in the range of 50.8-53.4 ppm and 28.6-30.2 ppm reported¹⁵ for several *trans* benzo[a]quinolizidines, while C₆ is shifted to $\delta < 46$ ppm in the *cis* II conformation and C₇ to $\delta < 26$ ppm in the *cis* III conformation.

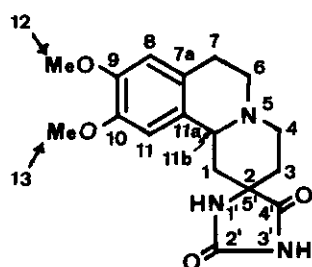


Table 2

^{13}C -nmr Spectra of Compounds A and B^a

Position ^b	Compound A (Bucherer)		Compound B (Read)	
	δ	$^1J(^{13}\text{C-H})$	δ	$^1J(^{13}\text{C-H})$
C ₇	29.85 (t)	128	29.89 (t)	128
C ₃	33.73 (t)	129	34.39 (t)	130
C ₁	39.87 (t)	131	40.44 (t)	130
C ₄ [*]	52.26 (t)	c	51.98 (t)	131
C ₆ [*]	52.60 (t)	c	51.98 (t)	131
C ₁₂ [†]	56.18 (q)	144	56.04 (q)	143
C ₁₃ [†]	56.56 (q)	144	56.43 (q)	144
C _{11b}	58.89 (d)	130	57.99 (d)	131
C ₂ (C ₅)	63.80 (s)	-	60.95 (s)	-
C ₈	113.12 (d)	153	113.01 (d)	147
C ₁₁	110.03 (d)	153	110.02 (d)	153
C _{11a}	130.01 (s)	-	130.36 (s)	-
C _{7a}	128.05 (s)	-	127.66 (s)	-
C ₉ [§]	148.58 (s)	-	148.49 (s)	-
C ₁₀ [§]	148.96 (s)	-	148.71 (s)	-
C _{2'}	158.67 (s) ^d	-	157.92 (s) ^e	-
C _{4'}	179.29 (s) ^f	-	179.95 (s) ^g	-

^aChemical shifts in ppm downfield TMS; J values in Hz.

^bCarbon signals marked in the table with *,[†] or [§] could not be assigned with certainty.

^cPoor resolution in spin-coupled spectrum.

^dHalf-width of peak without spin-decoupling 6 Hz.

^eHalf-width of peak without spin-decoupling 7.5 Hz.

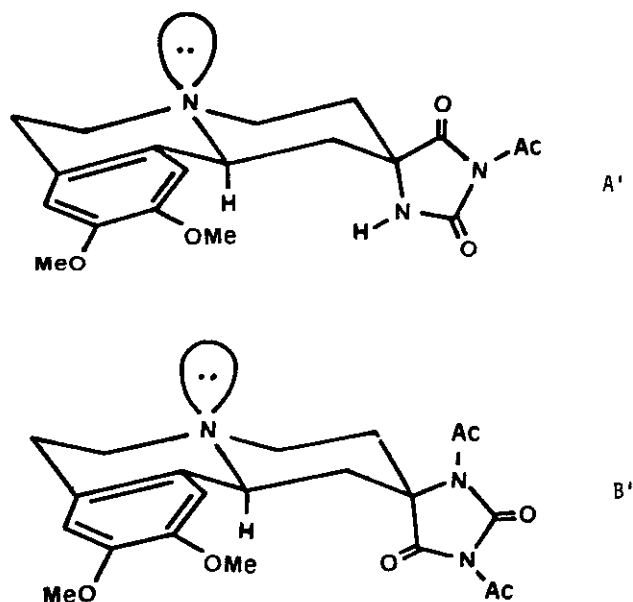
^fHalf-width of peak without spin-decoupling 11 Hz.

^gHalf-width of peak without spin-decoupling 18.5 Hz.

Once established the conformation of the benzo[a]quinolizidine ring system, the configuration of the spiranic carbon atom remains to be considered. The α and β spirohydantoin isomers must differ in the localization of the 4' carbon atom. In the α isomer, the 4' carbon is *gauche* with respect to all hydrogen atoms at C₁ and C₃, while in the β isomer it is *anti* with respect to two of them. Therefore the vicinal coupling constant $^3J(^{13}\text{C}-\text{H})$ must be greater and the ^{13}C peak broader in the β isomer than in the α isomer¹⁸.

The half-widths of signals for C₄, atoms in the proton-coupled spectra of A and B are shown in Table 2. From these data it may be concluded that the compound A has the α configuration while compound B should be identified with the β isomer. This outcome is in concordance with the Edward-Jitransgri rule.

In order to provide further confirmation for the results outlined above, compounds A and B were treated with acetic anhydride. While B was diacetylated to B' after a 9 h reflux, A was only monoacetylated (to A') even when the reaction time was prolonged to 17 h. In the α isomer, N₁, is placed in a much more hindered position than in the β isomer; therefore, the results of the acetylation experiments confirm the assignation of the α structure to A and the β to B.



The ascription of the β structure to compound B allows an easy interpretation of the anomalous shift of C_{11b} proton in the ^1H -nmr spectrum, which can be attributed to the deshielding effect of C₄, carbonyl group of the hydantoin ring. The δ value of 4.4 ppm (Table 1) is displaced about 0.8 ppm downfield in the B isomer from the expected value for a *trans* conformer¹¹. The difference in chemical

shift between β and α compounds is similar to the deshielding reportedly induced by the hydantoin $C_4=O$ group on β protons in compounds structurally related to B^{19,20}. This line of reasoning permits an independent assignment of structure β to compound B.

EXPERIMENTAL

Melting points are uncorrected and were obtained on a Büchi apparatus. Spectral data were recorded on the following spectrometers: ir—Perkin Elmer 577; 1H -nmr—Hitachi-Perkin Elmer R-24 (60 MHz) (compounds A' and B') and Bruker WM-200-SY (200.16 MHz) (compounds A and B); ^{13}C -nmr—Bruker WM-200-SY (50.32 MHz). All chemical shifts are referred to TMS. All coupling constants are given in Hz and correspond to the first order analysis of the spectra.

3'-Acetyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydrospiro[benzo[a]quinolizin-2,5'-imidazolidine]-2',4'-dione. A mixture of A (100 mg) and acetic anhydride (5 ml) was refluxed for 17 h in an oil bath at 150°C. The solvent was evaporated under reduced pressure and the residue crystallized from MeOH and charcoal, yielding 20 mg (18 %) of A'. Mp 244–246°C (MeOH). IR (KBr) cm^{-1} : 3400 (N-H), 1740, 1680, 1650 (C=O). 1H -nmr (d_6 -DMSO) δ : 6.60 (s, 2H, Ar-H), 4.50 (broad m, 1H, 11b-H), 3.70 (s, 6H, 2 OMe), 2.50 (s, 3H, COCH₃), 3.20–1.40 (m, 10H). Anal. Calcd. for $C_{19}H_{23}N_3O_5$: N, 11.26; C, 61.13; H, 6.17. Found: N, 11.01; C, 59.95; H, 6.03.

1',3'-Diacetyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydrospiro[benzo[a]quinolizin-2,5'-imidazolidine]-2',4'-dione. A mixture of B (100 mg) and acetic anhydride (5 ml) was refluxed for 9 h in an oil bath at 150°C. The solvent was evaporated under reduced pressure and the residue was crystallized from EtOH, yielding 70 mg (57 %) of B'. Mp 216–218°C (EtOH). IR (KBr) cm^{-1} : 1790, 1740, 1675, 1640 (C=O). 1H -nmr (d_6 -DMSO) δ : 6.70 (s, 1H, Ar-H), 6.65 (s, 1H, Ar-H), 3.80 (m, 1H, 11b-H), 3.70 (s, 6H, 2 OMe), 2.55 (s, 3H, COCH₃), 2.40 (s, 3H, COCH₃), 3.30–1.50 (m, 10H). Anal. Calcd. for $C_{21}H_{25}N_3O_6$: N, 10.12; C, 60.72; H, 6.02. Found: N, 9.92; C, 60.51; H, 5.92.

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