

## The Stereochemical Assignments of the Four 8-Azaestrone Configurational Isomers

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Complete correlation has now been accomplished for the four possible isomers in the 8-azaestrone series, synthesized by two different synthetic routes.

In recent years, much work has been directed toward the total synthesis of azasteroids. In our laboratories, this work has resulted in the synthesis, *via* two different synthetic routes, of all four stereoisomers of the tetracyclic nucleus of the 8-azasteroids (2,3). In this report we summarize the accumulated data which now allow firm configurational assignments and in the process correct erroneous assignments made earlier on the basis of less complete data (4).

Since the 8-azasteroid nucleus has not, to date, been found in naturally occurring substances, no correlation with known systems was possible, and stereochemical assignments were based originally on spectroscopic information previously known for related structures. Specifically, the infrared studies by Bohlmann (5) and Wenkert (6) on *cis* and *trans*-quinolizidines provided a useful guide to the BC stereochemistry of the 8-azasteroids, whereas the nmr studies of Uskokovic (7) and Bhacca and Williams (8) served as a basis for assigning BC-stereochemistry and orientation of the C-13 methyl group, respectively. In light of the evidence now in hand (9,10), it becomes apparent in retrospect that the Bhacca-Williams correlation does not hold in 8-azasteroids as it did in carbocyclic steroids.

The synthetic sequences have been described in detail elsewhere, but are reviewed in Chart I since method of synthesis became, in hindsight, crucial to the correction of configurational assignments. The four stereoisomers of the tetracyclic nucleus are drawn in their revised and now rigorously established configurations.

The spectral data for the four isomers is summarized in Table I. For isomer **4a**, the sole product of reduction of *trans* quaternary salt **7**, the upfield signal for the C-9 proton and the upfield shift for the C-13 methyl signal in benzene relative to chloroform led to the original and still correct *anti-trans* (11) assignment. This was later confirmed by single crystal X-ray analysis (9) on the 4-hydroxy derivative.

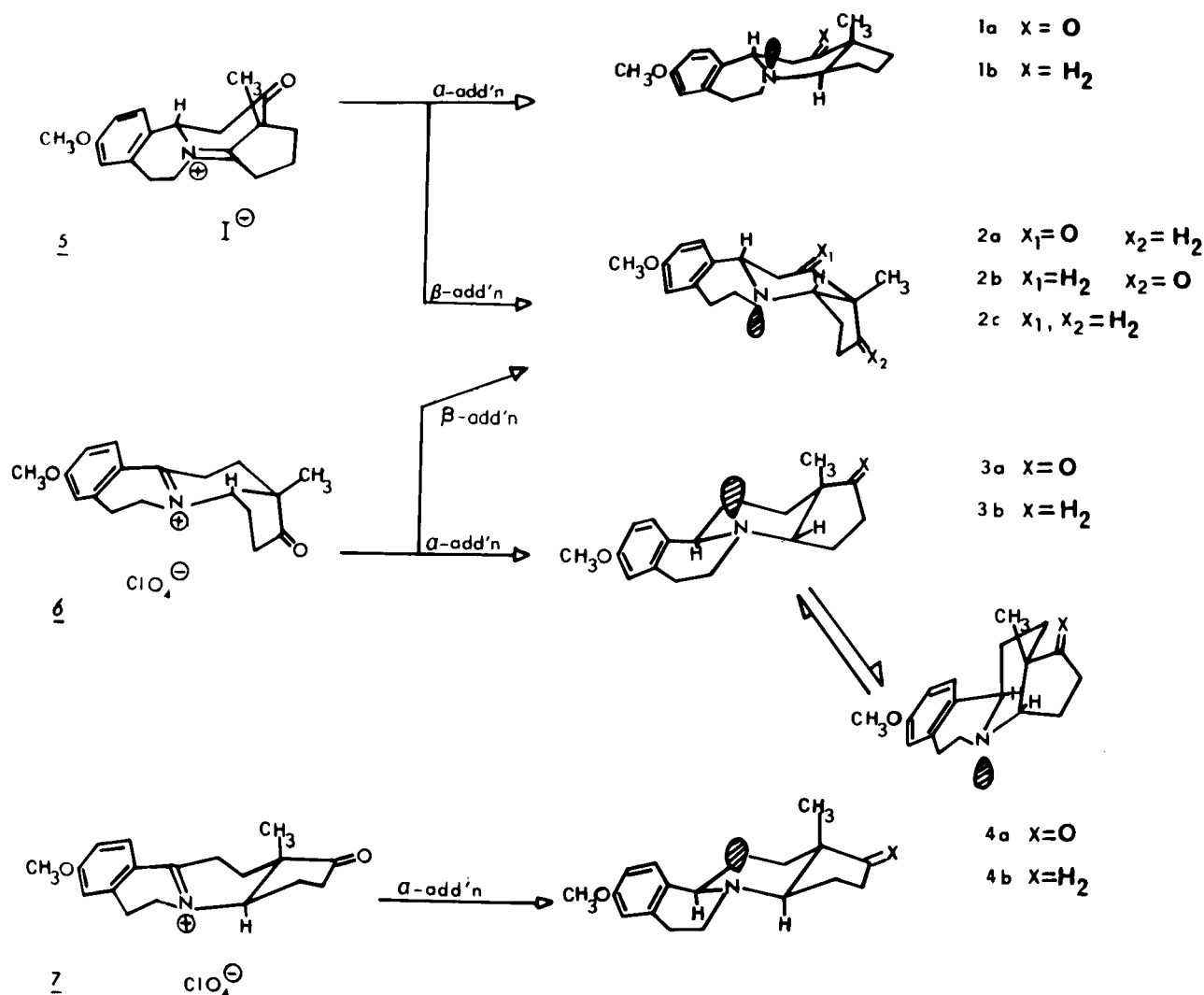
For the two CD *cis* bases, **2b** and **3a**, obtained by reduction of *cis* quaternary salt **6**, incorrect assignments were made (2) on the basis of the Bhacca-Williams correlation. Thus an upfield shift of 0.24 ppm and a downfield shift of 0.04 ppm on passing from chloroform to benzene indicated an axial methyl for the former and an equatorial methyl for the latter. As will be discussed below, it is now clear that the reverse is true for these two compounds, and they are now correctly re-assigned as given in Chart I.

Isomer **1a** was obtained, along with **2a**, by reduction of quaternary salt **5** and was incorrectly assigned initially as a stable conformer of configuration **4**. Single crystal X-ray analysis (10) of this product proved it to be the previously undescribed fourth isomer, **1a**, (of *syn-trans* configuration). For this product, the absence of Bohlmann-Wenkert bands and the downfield signal for the C-9 proton were consistent with the required *cis*-quinolizidine conformation.

TABLE I

NMR and Infrared Data for the Four Configurational Isomers of 8-Azaestrone Derivatives

Compound (Configuration)	Bohlmann- Wenkert Bands	C-18 ( $\delta$ )			
		C-9H ( $\delta$ )	CDCl <sub>3</sub>	C <sub>6</sub> H <sub>6</sub>	$\Delta$ C-18
<b>1a</b> ( <i>syn-trans</i> )	-	4.6	1.20	1.10	0.10
<b>2b</b> ( <i>syn-trans</i> )	-	4.2	0.95		
<b>2a</b> ( <i>syn-cis</i> )	+	3.8	1.22	1.04	0.18
<b>2b</b> ( <i>syn-cis</i> )	+	3.2	1.00	0.76	0.24
<b>2c</b> ( <i>syn-cis</i> )	+	3.2	0.95		
<b>3a</b> ( <i>anti-cis</i> )	-	3.8	1.17	1.21	-0.04
<b>3b</b> ( <i>anti-cis</i> )	-	3.6	1.13		
<b>4a</b> ( <i>anti-trans</i> )	+	3.2	1.02	0.90	0.12
<b>4b</b> ( <i>anti-trans</i> )	+	3.1	0.87		



With the configuration of **1a** established unequivocally as *syn-trans* from single crystal data, it followed that **2a**, the second product of the reduction of **5**, must also have a *syn* relationship (12) between the C-9 hydrogen and C-13 methyl. Wolff-Kishner reduction of **2a** afforded **2c**, which was identical to the product of Wolff-Kishner reduction of **2b**. Thus, through the desoxo product **2c**, the two synthetic routes were merged and **2b** must also have *syn* C-9 and C-13 substituents and be the *syn-cis* isomer. This left **3a** as the *anti-cis* isomer. These two configurations represent reversals of the assignments made in the previous work (2) on the basis of Bohlmann-Wenkert bands and the Baccia-Williams correlation (13), and that work stands corrected by this report. It is apparent that for **2**, the upfield signal for C-9 is consistent with the *trans*-quinolizidine conformation shown, whereas for **3**, the signal for C-9 is found in the 3.6-3.8 ppm range. This value is about

midway between the chemical shifts observed for the pure *trans*-quinolizidine compounds (**2** and **4**) and the pure *cis*-quinolizidine compound (**1**). This is interpreted as due to a conformational equilibrium as shown in the diagram (14,15).

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(11) The terms, *syn* and *anti* refer to the relationship between the C-9 and C-13 substituents.

(12) Likewise, the X-ray study of **1a**, established the *syn* relationships between the C-9 hydrogen and C-13 methyl in imminium salt **6**.

(13) It is apparent that the present work represents an exception to the Bhacca-Williams correlation, which, while found to be reliable in carbocyclic steroids, did not hold in the 8-azasteroids where

the chemical shift of the methyl group is subject to the anisotropic effect of the nitrogen lone pair.

(14) In the previous paper (2), this product had been assigned as a conformational equilibrium of the *syn-cis* configuration on the basis of the nmr observation and mercuric acetate oxidation experiments. The same arguments for a conformational equilibrium are applicable to the *anti-cis* configuration (**3**), since both configurations can exist in one *trans* and two *cis* all-chair conformations (2).

(15) It was suggested (4) that the new assignments for the two C-D *cis* bases (**2b**, **3a**) are consistent with a conformational analysis of the systems. In fact, this had been done in the original preliminary report on this work before the Bhacca-Williams correlation came to light [cf. R. I. Meltzer, D. M. Lustgarten, R. J. Stanaback and R. E. Brown, *Tetrahedron Letters*, 1581 (1963)].