Synthesis of New Heterocycles of the Benzo[*a*]quinolizine Group V. Synthesis of the 1-Methylhexahydrobenzo[*a*]quinolizin-2-ones. Preparation of the *cis*-Junction Isomer

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The reaction of 3,4-dihydro-6,7-dimethoxyisoquinoline hydrochloride on ethyl vinyl ketone yields two *cis* and *trans* benzo[*a*]quinolizinone isomers in variable proportions depending on the *p*H of the reacting medium. The *cis* junction isomer can be stabilized and isolated as the β-propionylethylquinolizinium chloride quaternary salt.

Introduction

Benzoquinolizidines can exist in either *trans* or in one of the two possible *cis* forms. The preferred conformation has a *trans* junction of the B and C rings with the nitrogen doublet in the *trans* diaxial position with respect to the C_{11b} proton; the two less favourable conformations have a *cis* junction with the lone electron pair of the tertiary nitrogen atom "gauche" or skew with respect to the C_{11b} proton. The characteristics of the infrared (2) and nmr (3) spectra of the isomers make differentiation of the three possible isomers.

The benzo[*a*]quinolizin-2-ones are usually found with the more stable *trans* junction.

In the course of our work on compounds of this series, we were led to prepare derivatives with a methyl group in the 1 position; in the present particular case, the formation of ring C is diastereogenic with respect to the carbon atoms C_1 and C_{11b} and it was shown (4) that a specific junction corresponded to each diastereoisomer.

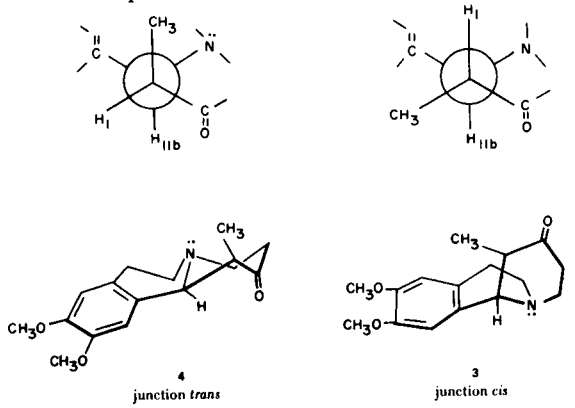


Figure 1

In the present paper, it will be shown that the two compounds are in equilibrium and that the least stable of the two isomers is the one which is formed most rapidly; this has made it possible to find the best suited experimental conditions to its preparation and isolation from the reacting medium.

We first prepared the *trans* 1-methyl-2-oxo-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizine (**4**) (Figure 2) by heating 3,4-dihydro-6,7-dimethoxyisoquinoline hydrochloride (**1**) in an excess of ethyl vinyl ketone (5,6). Ketone **4** (axial methyl group and *trans* junction; *cf.* Figure 2) was thus obtained in good yields (7). In the course of this preparation, very small quantities of isomer **3** (equatorial methyl group, *cis* junction) were also obtained. A tlc investigation of the course of the reaction revealed that the cyclization of the immonium salt **2** first yielded the ketone **3** which is transformed by heating into the thermodynamically more stable isomer **4**. It was therefore expected that

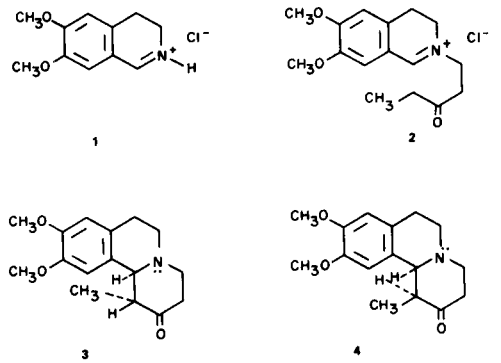
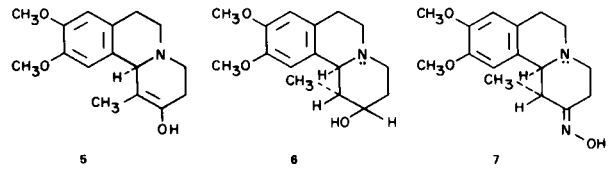


Figure 2

experimental conditions could be found which would slow the transformation of **3**, the less stable isomer, into **4** and allow its isolation. We thus prepared the compound at room temperature, in an aqueous solution at *p*H 7.7 since it is known (8) that the reaction does not occur at a much higher *p*H and that benzoquinolizinones partially regress to the immonium salt **2** when the *p*H is too low. Under these conditions, we obtained an 80% yield of a mixture of the ketones **3** and **4** though the proportions were such that the ketone **3** was difficult to separate. Its nmr spectrum shows a doublet centered at 3.6 δ attributable to the angular 11b proton of the *cis* quinolizine form. This signal integrates for 0.7 H. Thus 70% *cis* and 30% *trans* forms are present in this mixture. Furthermore, results of tlc and nmr studies showed that an equilibrium exists between the two isomers. Either **3** or **4** both give, in solution, a mixture containing 80% of the *trans* and 20% of the *cis* isomer as measured by nmr This is, in particular, the case at *p*H 7.7, hence the high percentage of the *trans* ketone obtained during the preparation.

It can be assumed that the transformation of one form into the other occurs through the enol form **5**. Indeed, we have found no isomerisation in compounds **6** and **7** in which the carbonyl group was replaced by a hydroxy or hydroxy-imino group. This was confirmed by the nmr spectrum of the equilibrium mixture from the *cis* ketone **3** in the presence of sodium deuteroxide: the signal from the methyl group in the *trans* ketone **4** has become a singlet at 0.95 δ. This can be explained by the deuteration of the intermediate enol **5** which leads to the ketone **4** deuterated at C_1.



5 6 7

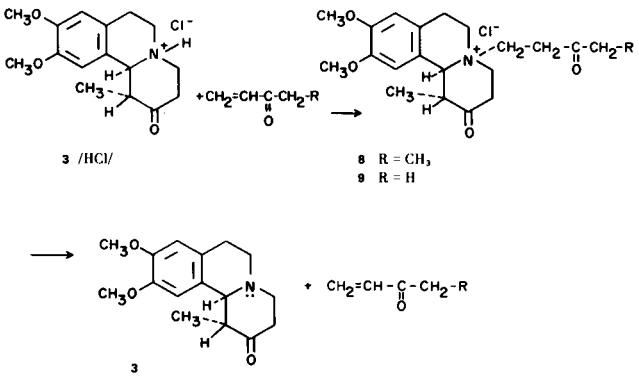
A series of trials performed at various buffered *p*H and monitored by tlc showed that the best yield of the pure *cis* isomer is obtained at *p*H = 7.35. Even though, in that case, there remains some non-cyclised immonium salt **2**, ketone **3** can be isolated 27% yield.

In the course of this aforementioned synthesis, we also isolated a new compound **8** (Figure 3). Its structure was determined from the following facts:

The analytical results showed that the compound contains two molecules of ethyl vinyl ketone for each molecule of 3,4-dihydro-6,7-dimethoxyisoquinoline, and a single chlorine ion. This last fact, together with the high solubility in water and the polar behaviour in tlc, render the quaternary ammonium salt structure highly probable.

In alkaline solution, compound **8** rapidly breaks down, giving one molecule each of ketone **3** and of ethyl vinyl ketone which was detected by vpc. This case of elimination is characteristic of quaternised Mannich base salts.

Lastly, the nmr spectrum fully confirms the structure advanced. It shows the triplet due to the propionyl methyl group at 1.09 δ and a doublet from the methyl group at C_1 at 1.645 δ. The doublet at 4.50 δ can be attributed to the proton at C_{11b} since decoupling at 1.645 δ enables the C_1 proton to be found at 2.51 δ while decoupling at 2.51 δ annuls the multiplets at 4.50 δ and 1.645 δ. The value $J_{1\text{-}11b}$ = 10 Hz for the coupling constant is characteristic of a *trans* diaxial coupling (3); this entails both a *cis* conformation for the molecule and an equatorial position for the C_1 methyl group.



3 /HCl/ 8 R = CH_3, 9 R = H

Figure 3

When in its salt form, the tertiary amine **3** can react on the electrophilic double bond of the ethyl vinyl ketone; (9, 10) this reaction is made easier by the *cis* junction which decreases the steric bulk of the nitrogen atom. This is confirmed by the observation that **8** was obtained solely by reaction of the hydrochloride of **3** on the ketone while the corresponding attempt carried out with the hydrochloride of **4**, which has a *trans* junction, failed. This difference in reactivity in *cis* and *trans* junction compounds is fairly characteristic and can be illustrated by their difference in rate of methiodide formation, as followed by conductimetry (11): the value measured for **3** is 75 x 10^{-4} sec^{-1} while the value for **4** is only 0.37 x 10^{-4} sec^{-1}.

Conclusion

One can thus synthetize ketone **3** by a new route, namely the quantitative decomposition of **8** in alkaline medium; compound **8** is itself conveniently obtained in a pure form through the reaction of two moles of ethyl vinyl ketone on the hydrochloride of **1** at *p*H = 7.35. Also, benzo[*a*]quinolizinones **3** and **4** can be separated through the reaction of methyl vinyl ketone on a mixture of the hydrochlorides of isomers **3** and **4** since this last isomer is not affected while the first yields the crystalline benzo[*a*]-quinolizinium chloride **9**.

Generally speaking, it would appear that addition of an alkyl vinyl ketone to a mixture of *cis* and *trans* quinolizines might be a particularly valuable method of separation of these isomers when their rates of quaternization are sufficiently different.

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EXPERIMENTAL

Ir spectra were recorded on a PE Infracord 257, nmr spectra on a Varian HA 100, vp chromatographs on an Aerograph Model 200. Microanalyses were performed at the Laboratoire de Chimie IV, Faculte des Sciences d'Orleans. Thin-layer chromatographies (after Stahl) were carried out on Kieselgel G and eluted with a methylene chloride-methanol 90-10 mixture.

cis 1-Methyl-2-oxo-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizine (**3**) and *trans* 1-Methyl-2-oxo-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizine (**4**).

A solution of 2.8 g. of 3,4-dihydro-6,7-dimethoxyisoquinoline hydrochloride in 10 ml. of water was brought to *p*H 7.7 with triethylamine; 0.9 ml. of ethyl vinyl ketone was added, the mixture was stirred for 3 hours, left overnight at room temperature and the precipitate was collected by filtration. After washing with water, 2.2 g. (80% yield) of a mixture of isomers **3** and **4** was obtained; nmr (deuteriochloroform): internal reference TMS, δ TMS = 0, ($C_{11b}H$, d, 3.6 δ, 0.7 H).

cis 1-Methyl-2-oxo-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b-*H*-benzo[*a*]quinolizine (**3**).

A solution of 1.8 g. of 3,4-dihydro-6,7-dimethoxyisoquinoline in 8 ml. of water cooled in ice was brought to *p*H 7.35 with triethylamine. Ethyl vinyl ketone (0.85 g.) was added and the mixture was left overnight at room temperature. The precipitate was collected and washed with water. After recrystallization from a diisopropylether-ethanol mixture, 0.6 g. (27.5%) of the pure ketone **3** was obtained, m.p. 130°, m.p. (Kofler block) 136°. After a few days, the mother liquor spontaneously yielded 0.05 g. of *cis* 1-methyl-2-oxo-5-β-propionylethyl-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizinium chloride (**8**) m.p. 251°; ir (potassium bromide): 3580, 3130 cm^{-1}; (C=O) ketone 1705 cm^{-1}; nmr (deuterium oxide): internal reference TSS, δTSS = 0, 2 aromatic H, 6.93 and 6.86 δ; C_{11b} H, d, 4.50 δ; C_1CH_3, d, 1.645 δ; propionyl CH_3, t, 1.09 δ.

Anal. Calcd. for $C_{21}H_{30}O_4NCl$: C, 63.70; H, 7.63; N, 3.53. Found: C, 63.65; H, 7.62; N, 3.36.

cis 1-methyl-2-oxo-5-β-propionylethyl-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizinium Chloride (**8**).

A solution of 7.5 g. of 3,4-dihydro-6,7-dimethoxyisoquinoline hydrochloride in 15 ml. of water, cooled in ice, was brought to *p*H 7.35 with triethylamine. Ethyl vinyl ketone (7.5 ml.) was added and the mixture stirred at room temperature for 7 hours. After leaving overnight, the precipitate was collected, washed and recrystallized from absolute ethanol, yield: 4.5 g. (34%) of **8**.

Ethyl vinyl ketone (0.2 ml.) was added to a solution of 0.25 g. of **3** in a mixture of 2 ml. of water and 0.175 ml. of 4*N* hydrochloric acid. The mixture was stirred for 48 hours and evaporated until dry under reduced pressure. The solid white residue was suspended in absolute ethanol, filtered off and washed with absolute ethanol, yield, 0.18 g. (62%) of pure **8**.

Compound **3** from compound **8**.

A stirred and ice cooled solution of 1.6 g. of **8** in 24 ml. of water was brought to *p*H 10 with 10% sodium hydroxide. The crystalline precipitate **3** was collected and washed with water to give 1 g. (90%) of **3**. This reaction has been followed by vpc (10% Carbowax 20 M, 1/8", 10 ft. column, temperature: 200° nitrogen flow 30 ml. per minute). After injection of an ethylene glycol solution of **8** and triethylamine, the characteristic peak of ethyl vinyl ketonewas observed. Equilibrium between **3** and **4** was obtained after 30 minutes at 33° in basic solution; nmr (deuteriomethanol, sodium deuteroxide) internal reference TMS, δ TMS = 0,C_1 CH_3, d, 1.07 δ 20% *cis* form; C_1CH_3, s, 0.96 δ, 80% *trans* form.

Separation of an Equimolecular Mixture of **3** and **4**.

A suspension of 0.4 g. each of **3** and **4** in 4.6 ml. of 0.6*N* hydrochloric acid was stirred with 0.4 ml. of freshly distilled methyl vinyl ketone for 18 hours. The solution thus obtained was evaporated to dryness under reduced pressure. Recrystallization from absolute ethanol repeatedly yielded 0.3 g. of **9** and 0.3 g. of the hydrochloride of **4**.

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