BENZO- AND INDOLOQUINOLIZINE DERIVATIVES XX[1].

SYNTHESIS AND CONFORMATION OF 5,6,8,9-TETRAHYDRO-13bH-DIBENZO[a,h]QUINOLIZINE AND 5,6,8,9,14,14b-HEXAHYDROBENZO[a]INDOLO[3,2-h]QUINOLIZINE.

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Abstract - Dibenzo[a,h]quinolizidines are prepared by an imminium cyclization or by PPA cyclization of the ethyleneoxide adduct of 1,2,3,4-tetrahydro-1-phenylisoquinoline. The conformational equilibrium in the title compounds is studied by ^{13}C NMR.

Dibenzo[a,h]quinolizine derivatives have received little attention compared to the dibenzo [a,g]isomers. The earliest claims for the synthesis of compounds 1c,d by cyclization of the 3,4-dihydroisoquinolinium salts 2[2] or of the 3,4-dihydroisocarbostyril 3[3] were shown to be incorrect. These compounds could nevertheless be obtained from 3[4] or by ring closure of the aldoximes 4[6], followed by reduction. The best yields are obtained by cyclization of the hydroxyamids 5[7].

The failure of 2c,d to cyclise to 1c,d as reported in the literature is due to the absence of acid catalyst in the reaction medium. In our hands, 2c cyclises quantitatively to 1c in 6N hydrochloric acid. Moreover the preparation of the iminium compound 2c proceeds in high yield from homoveratrylamine and 2-(2-bromoethyl)benzaldehyde.

It is known that an unsubstituted phenyl as in 2a is not reactive enough to lead to 1a, nor can it be cyclised in a Bishler-Napieralski reaction[5]. The parent compound 1a was therefore prepared starting from 1,2,3,4-tetrahydro-1-phenylisoquinoline 6, which on reaction with ethylene-oxide gives 7 in 95% yield. The latter was cyclised in polyphosphoric acid to 1a in 75% yield. The alkylation of 6 with either dibromoethane or 2-bromoethanol resulted only in HBr elimination.

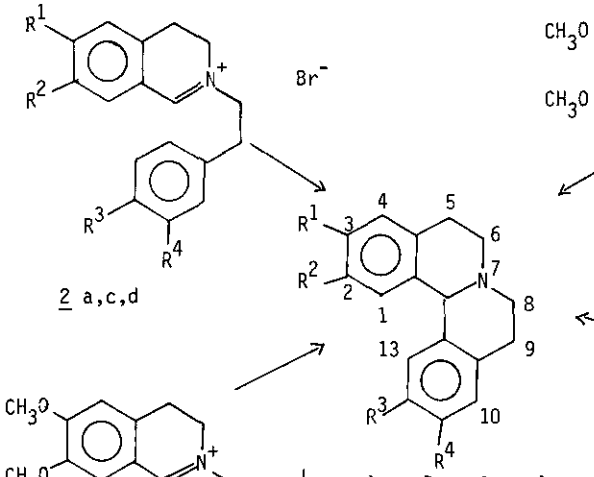
Benzo-substituted quinolizidines can exist in conformational equilibrium between a trans- and two cis-forms. In the case of dibenzo[a,h]substitution (R_1=R_4, R_2=R_3), both cis conformations are

identical and are interconvertible by a cis-decalin type ring inversion.

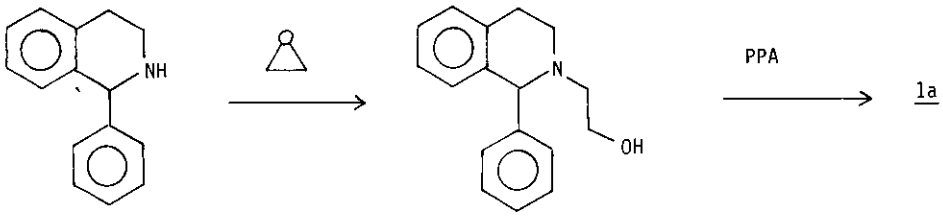
For the tetramethoxy-compound 1d, the trans stereochemistry was proposed on the basis of its ease of dehydrogenation with mercuric acetate, and of its simple proton NMR spectrum for the methylene protons[6]. No Bohlmann i.r. bands were observed. However, the C5 and C6 protons in the trans conformation are nonequivalent and should give a complex proton spectrum[8,9]. By assuming a rapid equilibrium between the equivalent cis conformations, the averaged spectrum of an AA'BB' type can be explained.

The cis stereochemistry is further confirmed by the carbon-13 NMR spectrum. It has been shown that the chemical shifts of C5 and C6 in benzo[a]quinolizidines are characteristic of the ring fusion[10,11]. For the cis_1 conformation, C5 and C6 are expected to resonate at $\delta \approx 29$ ppm and $\delta \approx 46$ ppm respectively, whereas for the cis_2 conformation these values are 25 ppm and 51 ppm. As can be seen from table 1, the observed values for 1 are exactly averaged over these model values. This clearly indicates a rapid interconversion of the two cis conformers.

Reaction Schemes



	R^1	R^2	R^3	R^4
1a	H	H	H	H
b	OCH_3	OCH_3	H	H
c	H	H	OCH_3	OCH_3
d	OCH_3	OCH_3	OCH_3	OCH_3
e	OCH_3	OCH_3	$O\text{-}CH_2\text{-}O$	
f	$OCH_2C_6H_5$	OCH_3	H	H
g	OCH_3	H	H	H



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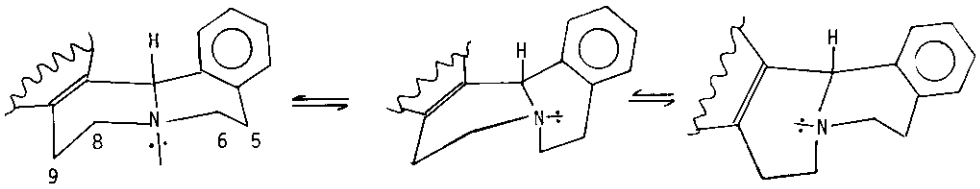
Conformational equilibrium in benzoquinolizidines



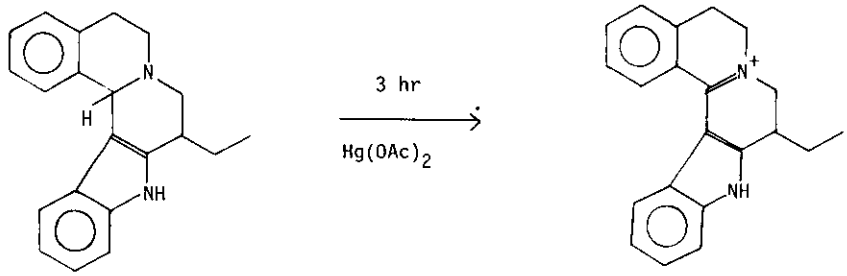


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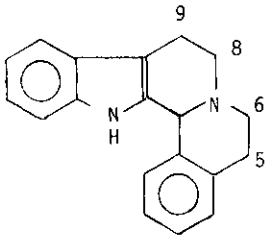
TABLE 1

^{13}C Chemical shifts of dibenzo[a,h]quinolizidines 1

	δ C5	C6	C8	C9	C13b
1a	26.3	47.3	47.3	26.3	60.9
1c	26.6	47.6	47.0	26.0	60.1
1d	26.7	48.0	48.0	26.7	60.7

Despite their cis stereochemistry these compounds are rapidly oxidized by mercuric acetate[6]. This must be ascribed to the enhanced acidity of the 13b proton. A similar oxidation was observed in an indole analog 8 of 1 by Gerzberg[12]. For 8 a cis_1 stereochemistry was proposed.



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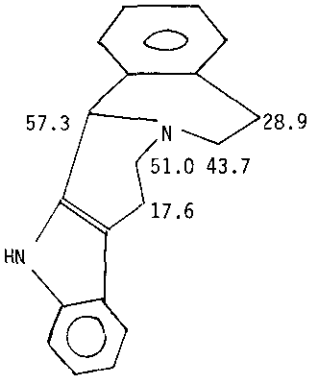

10(cis_1)

We could confirm this stereochemistry for 5,6,8,9,14,14b-hexahydrobenz[h]indolo[2,3-a]quinolizine 9[13]. The carbon-13 chemical shifts of C5 and C7 indicate a preferential cis_1 conformation 10[10,14].

EXPERIMENTAL

^1H NMR spectra were recorded on a Bruker HX270, ^{13}C NMR spectra were recorded on a Bruker WH90 apparatus. Solutions were in $CDCl_3$ with tetramethylsilane as internal reference. IR spectra were measured with a Perkin Elmer 257 spectrometer and mass spectra with a AEI MS 902S spectrometer.

- 2-[2-(3,4-Dimethoxyphenyl)ethyl]-3,4-dihydroisoquinolinium bromide 2c

To a solution of 4.75 g 2-(2-bromoethyl)benzaldehyde[15] in 50 ml dioxane, 5 g homoveratrylamine in 50 ml dioxane are added dropwise with mechanical stirring. After 20 min, the precipitate is collected and crystallized from ethanol. Yield : 85%, m.p. 197°, ir : 1660 cm^{-1} ($C=N^+$), ms : m/e 295 (M^+, 10%), 151 (37%), 146 (51%), 144 (100%).

- 2,3-Dimethoxydibenzo[a,h]quinolizidine 1b

1.9 Grams of 11 are heated in 50 ml 6N HCl at 100° for 6 hours. After cooling, the solution is basified with 20% NaOH and extracted with ether. After drying and evaporating the solvent, 1b is obtained quantitatively.

m.p. (HCl, from ethanol) : 225-6°, nmr : 5.03 (s, H13b), 3.17 (multiplet, 4H).

- 2-(2-Hydroxyethyl)-1-phenyl-1,2,3,4-tetrahydroisoquinoline 7

In an autoclave, 5.3 g 1-phenyl-1,2,3,4-tetrahydroisoquinoline 6 in 400 ml absolute ethanol are cooled to -20°C. Then 3 ml ethyleneoxide are added. After sealing the autoclave, one heats at 75°C for 24 hours with magnetic stirring.

Then the solvent is evaporated and 7 is used as such in the next reaction step. It can also be crystallised from c-hexane, m.p. 69.5°, ir : 3380 (OH), nmr : 7.2-7.1 (9H arom.), 4.8 (H1), 3.6-2.4 (8H alif.).

- Dibenzo[a,h]quinolizidine 1a

1.18 Grams of crude 7 are heated with 25 g of polyphosphoric acid for 6 hours at 160° with mechanical stirring. After cooling the mixture is poured onto ice and extracted with ether. The water phase is basified and extracted with ether. This yields 75% overall yield for both steps.

m.p. (HCl) : 230-4°, ms : m/e 235 (66%), 234 (100%), 206 (26%), nmr : 5.08 (s, H13b), 3.17 (multiplet, 4H), 2.90 (multiplet, 4H).

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