BENZO- AND INDOLOQUINOLIZIDINES. PART XVIII[+].[#]

THE PREPARATION OF 4b,5,6,7,7a,9,10,14b-OCTAHYDRODIBENZO[*a,h*]CYCLOPENTA[*c*] QUINOLIZINE ISOMERS. AN APPLICATION OF STEREOSELECTIVE IMINIUM CYCLISATIONS.

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Title compounds were synthesized starting from either *cis*- or *trans*-2-phenyl-cyclopentylamine, leading to two types of iminium intermediates 4 and 7, which were cyclised upon heating in 6N hydrochloric acid solution. The configuration of the obtained isomers is discussed as a consequence of the stereo-controlled reaction pathway.

Iminium salts are highly reactive intermediates[2]. Their synthetic use in ring closures of aryl systems is well established[3,4]. In order to explore their applicability to the synthesis of the octahydrodibenzo[*a,h*]cyclopenta[*c*]quinolizine system and examine the stereochemical outcome of the reaction we prepared the title compounds.

trans-2-Phenylcyclopentylamine 1a (or the 3-methoxyphenylderivative 1b) was obtained in 40% overall yield by dropping 1-phenylcylopentene[5] to an equivalent amount of the borane-methyl sulfide complex in diglyme at room temperature, stirring the solution for 6 hours and subsequent addition of hydroxylamine-O-sufonic acid according to Brown's procedure[6]. (m.p. N-benzoyl derivative of 1a 162-63°[6], m.p. N-benzoyl derivative of 1b 97-98°) (Scheme 1).

Hydroboration-oxidation of the olefin to its corresponding alcohol 2 was carried out in 85% yield[7] (b.p. 89°/0.25 mm, b.p. 3-methoxyphenyl deriv. 174°/14 mm) Treatment of this *trans*-alcohol with an excess of tosyl chloride in pyridine, followed by standing for 4 days in a refrigerator gives quantitatively the tosylated compound (m.p. 65°, m.p. 3-methoxyphenyl deriv. 58-59°). The SN_2 displacement reaction with sodium azide in DMF at 100° for 48 hours leads to the crude azide

[+] for a preceeding paper see reference 1.

[#] Dedicated to Professor T. Nozoe on the occasion of his 77th birthday.

(ir. 2100 cm^{-1}), which was further reduced by dropwise addition to a stirred solution of lithium aluminium hydride in ether (4 hours). After work up the *cis*-amine 3 is obtained in 75% overall yield for both steps (m.p. N-benzoyl derivative of 3a 116.5-17.5°, m.p. N-benzoyl derivative of 3b 87-88°) (Scheme 2). The stereochemical purity of all compounds was checked by 270 MHz proton nmr analysis.

Condensation of the appropriate amine with an equimolar quantity of 2-(2-bromoethyl)benzaldehyde[8] in dioxane[9] gave the corresponding iminium bromide 4 in 60-70% yield (dec. *trans* 179-80°, *cis* 159-60°, ir. 1650 cm^{-1}). The salt 4 was refluxed for 48 hours in 6N hydrochloric acid. The reaction mixture was made alkaline, extracted (ether), dried and evaporated. The residue was passed over a short column (alumina/ether) to obtain the pure 3-methoxy-octahydrodibenzo[*a*,*h*]cyclopenta[*c*]quinolizine isomers 5 (Scheme 3). Yields and configurations of the products are listed in table 1.

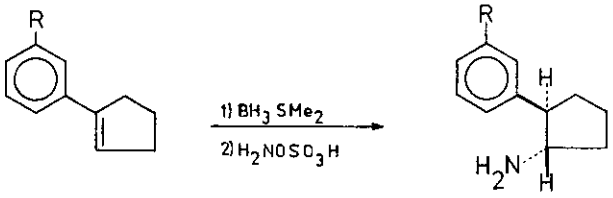
After reflux of the amine in ethyl formate in the presence of acid catalyst[10] and cyclisation of the resulting formamide in PPA (160°, 4 hours) one obtains the 2,3,3a,8b-tetrahydro-*1H*-cyclopenta[*c*]isoquinoline 6 (b.p. trans 82°/0.07 mm, b.p. cis 72°/1.5 mm, ir. 1620 cm^{-1}). Heating 6 and an equivalent amount of commercial 2-(3,4-dimethoxyphenyl)ethyl bromide for 3 hours at 100° without solvent leads in 65-70% to the iminium intermediate 7 (cryst. isopropanol dec. trans 186-87°, dec. cis 178-83°, ir. 1660 cm^{-1}) (Scheme 4). Cyclisation is performed as described for the intermediates 4 (see above), the results are collected in tabel 1.

TABLE 1

Compound	reaction time (hours)	yield %	isomer	dec. ($HClO_4$)
trans-4	48	50	+*rel*-(4bα,7aβ,14bβ)	156-63°
cis-4	48	90	*rel*-(4bα,7aα,14bβ)	169-72°
*trans*7	48	65	*rel*-(4bα,7aβ,14bα)	180-85°
cis-7	48	90	*rel*-(4bα,7aα,14bβ)	182-85°

+isomers are obtained as recamic mixtures, for nomenclature see Pure and Appl. Chem., 45, 13 (1976).

Scheme 1



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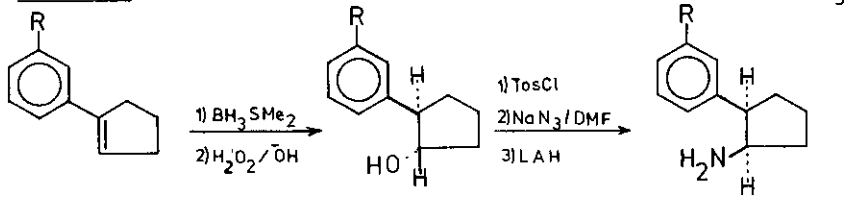
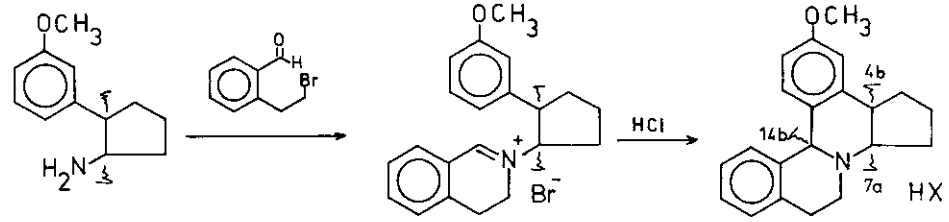
a) R = H
b) R = OCH_3

Scheme 2



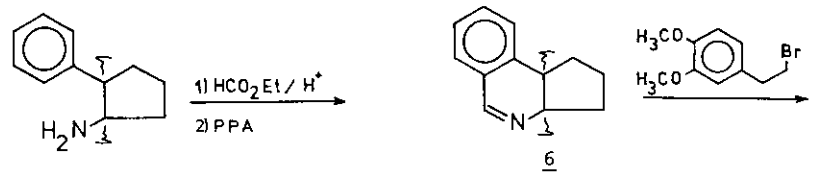
2 3

Scheme 3



4 5

Scheme 4



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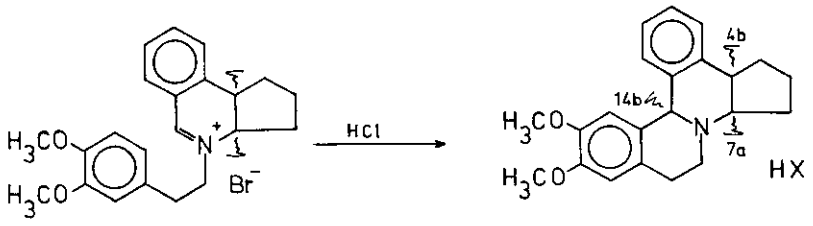


7 8

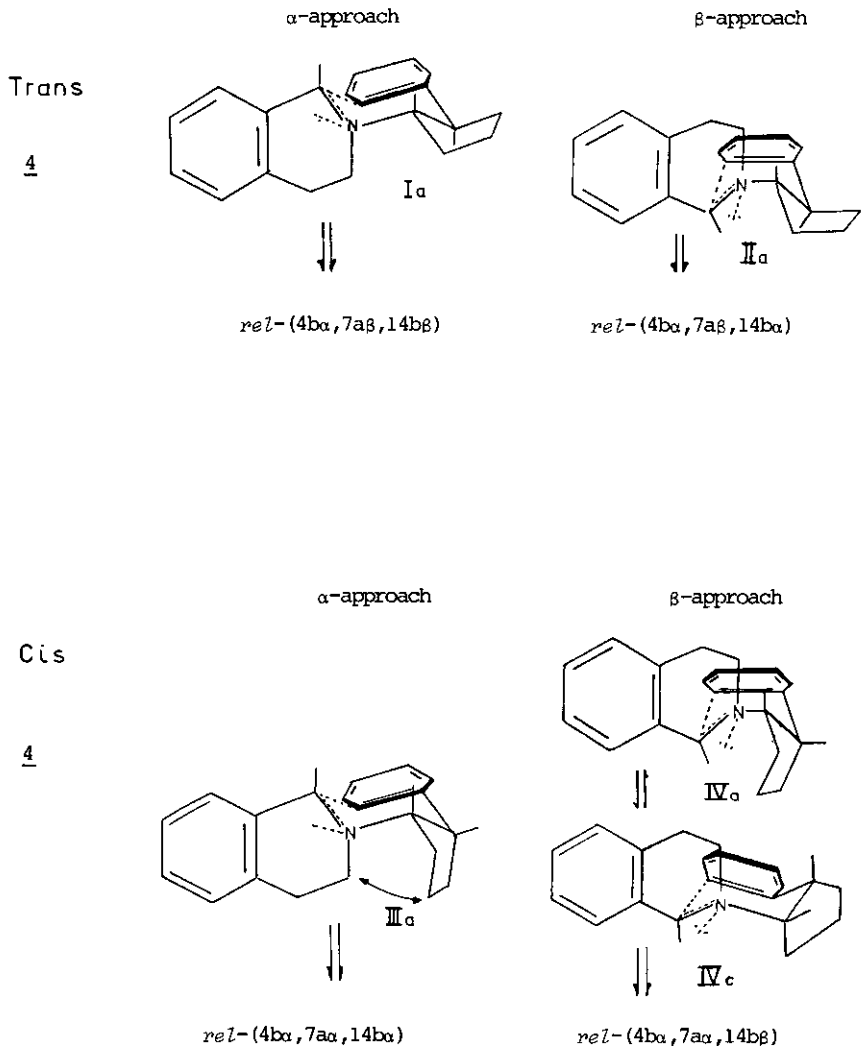
From the data described above (table 1) several conclusions can be drawn. A first interesting observation is the fact that the *cis*-compounds react cleaner, and therefore give higher yield, than the *trans*-compounds do. The latters had to be chromatographed (CH_2Cl_2/Alumina) prior to isolation as perchlorate salts, since some impurities were present. No trace of the other isomers was found in the reaction mixture (checked by ^1H nmr spectroscopy). Secondly a remarkable selectivity of the reaction occurs : Scheme 3 leads to the single *rel*-(4bα,7aβ,14bβ) isomer and Scheme 4 to the epimeric *rel*-(4bα,7aβ,14bα) isomer for the *trans* series, while both schemes lead to the same *rel*-(4bα,7aα,14bβ) isomer for the *cis* series. It is clear that only a stereoelectronically governed (synchronous) reaction mechanism in combination with secondary steric implications can be responsible for these results, since a two-step mechanism would give mixtures of isomers. Applying the Stork-Eschenmoser[11] hypothesis one can easily predict the stereochemical outcome of the cyclisation. This is also true for α-acyl iminium cyclisations on unactivated olefins[12].

If we assume that the nucleophile can approach the iminium system from two sides (α or β) we must first examine the possibility of a transition state in which the incoming nucleophile and developping nitrogen electron paire are anti-parallel disposed[11] and secondly look for possible steric interactions. For example in Scheme 3 for the *trans* series (figure 1) two possibilities for the transition state exist : an α-approach leads to Ia, with a chair geometry, while a β-approach leads to the unfavourable boat transition state IIa (dotted lines indicate the incoming nucleophile and developping electronpair), this favours the formation of the *rel*-(4bα,7aβ,14bβ) isomer. If the same cyclisation is applied to the *cis* compound, the α-approach leads to severe steric interactions (as indicated by an arrow) between the hydrogens on carbons 6 and 9, the β-approach on the contrary is no longer boat since IVa can easily convert to IVc by inversion of the five membred ring. Therefore this route is preferred and the *rel*-(4bα,7aα,14bβ) isomer results.

In Scheme 4 (figure 2) the situation is reversed for the *trans* product : an α-approach now leads to an unfavourable boat conformation Ib (N8-C9 and C7-C7a eclipsed), while a β-approach gives the chair transition state IIb. Therefore the *rel*-(4bα,7aβ,14bα) isomer is obtained. In the series the unfavourable boat conformation IIIb can again be inverted to the chair transition state IIIc, which contains however strong steric interactions between C7a and C10, while a β-approach leads to the favourable IVb transition state and so to the corresponding *rel*-(4bα, 7aα, 14bβ) isomer. (Notice that Ia and Ib are in fact the conformers of the same isomer, as well as IIa $\rightleftharpoons$ IIb, IIIa $\rightleftharpoons$ IIIc $\rightleftharpoons$ IIIb, and IVa $\rightleftharpoons$ IVc $\rightleftharpoons$ IVb). So the theoretical predictions parallel

Figure 1

Scheme 3



(methoxy substituents were avoided)

Figure 2

Scheme 4

Trans

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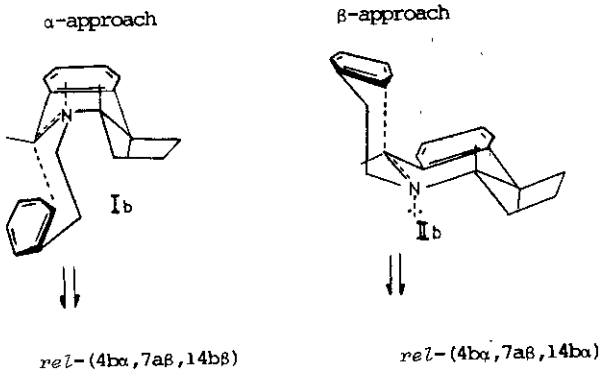

Cis

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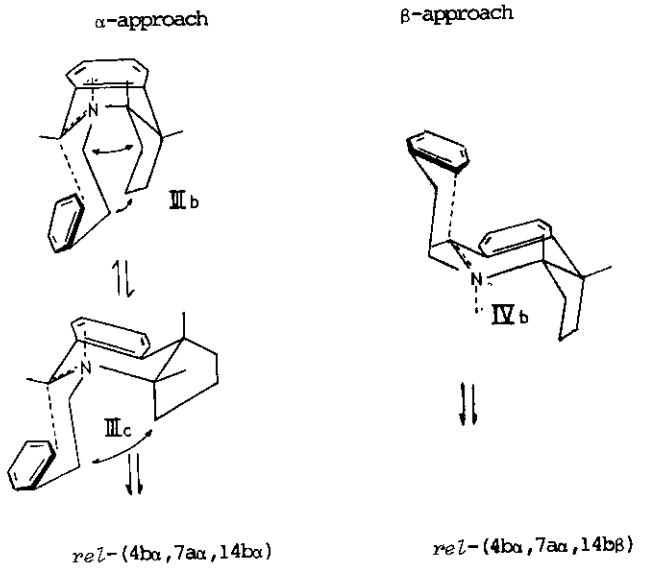

(methoxy substituents were avoided)

completely the experimental findings.

The configurations of the compounds was determined by ir and nmr spectroscopy, as were the preferred conformations which are not for all compounds identical with the kinetically formed transition states[13].

ACKNOWLEDGEMENTS

We are indebted to the "Fonds voor Kollektief en Fundamenteel Onderzoek" and the "Nationale Raad voor Wetenschapsbeleid" for their financial support. We thank the "Instituut ter aanmoediging van het Wetenschappelijk Onderzoek in Nijverheid en Landbouw" for a grant to one of us (F.V.).

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Received, 26th September, 1978