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SYNTHESIS OF ANALOGUES OF CRYPTOPLEURINE—II[1]

NUCLEOPHILIC ELIMINATION OF PHENANTHRO-QUINOLIZIDINE ALCOHOLS

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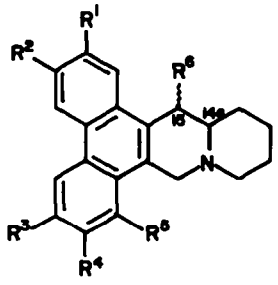
Abstract—The authors studied nucleophilic elimination in n-amyl alcohol of epimeric phenanthroquinolizidine alcohols, in the presence of potassium n-amylate, at 130°. Conclusions were drawn from the relative velocity of transformation of epimers upon the *cis*-mechanism of the elimination and from PMR measurements upon the conformation of olefin formed.

In a previous paper[1] the authors described the preparation and determination of configuration of epimeric phenanthroquinolizidine alcohols (1_A, 1_B) in the course of synthesising analogs of cryptopleurine (1: R^1, R^2, R^3, R^4, R^5 = H or OMe_3 R^6 = H, or OH).



1A: $R^1 - R^5$ = H, R^6 = OH(ax).
1B: $R^1 - R^5$ = H, R^6 = OH(equ.)
2: $R^1 - R^6$ = H, 14a-15 dehidro

For a further study of the properties of the epimers and to determine their relative thermodynamic stability isomerisation equilibrium experiments were carried out with both epimers.

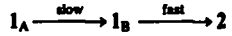
The isomerisation of epimeric alcohols was observed by Harris[2] in 1887. Thereafter several papers dealt with a detailed description of this phenomenon and clearing up the reaction mechanism.[3a–d] According to these the epimerisation of alcohols takes place via the splitting-off of H^- from the alpha C atom, then by recombination through a ketonic intermediate. However, under the conditions for equilibrium described in the literature, potassium-amylate in amyl alcohol at (130°) the $1_{A,B}$ epimers do not suffer the expected isomeric transformation but as a result of elimination they are transformed into olefin (2).

The elimination reaction is not a result of the thermal decomposition. This is proved by the negative result, i.e. lack of elimination, of an experiment carried out in amyl alcohol in the absence of potassium-amylate. Relying upon this finding, the elimination of alcohol can be regarded as a nucleophilic reaction catalysed by a base. As a rule, alcohols are dehydrated by basis catalysed in this way, i.e. by removal of H^+ from the α-C atom when there is a double bond between the γ and δ C atoms.

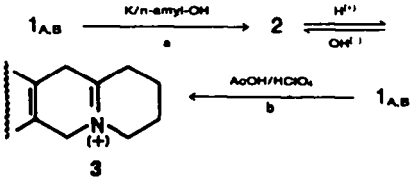
This condition is not fulfilled with the $1_{A,B}$ epimers but in the compound thus formed (2) the olefin bond is conjugated with the aromatic system. Probably the anellated tertiary C hydrogen plays a decisive role in the elimination, an idea supported by the fact that under the experimental conditions used at $1_{A,B}$ epimers, phenyl-methyl-carbinol (having a similar system) is not transformed into olefin by potassium-t-butoxide.[3b] There are references as to the nulceophilic elimination of alcohols where, beside the base, other reagents are used; e.g. KOH and $CHBr_3$ together start an elimination reaction, but the carbene formed as an intermediate product also takes part in the process[5a,b] or there is another dehydration process by preparing the alcoholate and treating it with $AlCl_3$.[5c] The peculiar behaviour of phenanthroquinolizidinol epimers ($1_{A,B}$) is shown furthermore in that they do not dehydrate in dimethyl-sulfoxide, while phenyl-methyl-carbinol is readily transformed into olefin under the same conditions.[5d]

The relative rate of transformations of the two epimers (1_A, 1_B) can yield some information about the unexpected reaction mechanism. Thus, the position of OH and the anellated proton in the epimers (1_A *trans*; 1_B *cis*) and their relative transformation rate suggests the favoured *cis*- and *trans*-eliminations, respectively. Under similar conditions 1_B transformed into olefin in 20 hr, while 1_A in 72 hr. It follows that in this transformation the *cis* elimination is the more favoured, probably taking place through a 4-centered transition state, similar to processes with multy centered reactions as described with dehydro halogenation and other reactions.[6]

However, from the rate conditions of transformation of the epimers it is not unequivocal that both reactions take place though at different rates. Namely, under the experimental conditions applied it must be supposed that it is the thermodynamically unstable isomer (1_A) that epimerised into the more stable isomer (1_B) at first and the elimination step followed thereafter. Considering, however, that the reaction rate of the following step ($1_B \rightarrow 2$) is higher than that of the previous one ($1_A \rightarrow 1_B$)—i.e. 1_B is formed slower than it disappears—the isomerisation could not be detected reliably by tlc. Considering all these, the transformation of the less stable isomer can be described by the reaction Scheme 1.



Scheme 1.



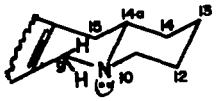
Scheme 2.

The structure of olefin formed during the elimination (2) was identified by analysis, IR and PMR spectroscopy, and by comparison with an authentic sample (reaction Scheme 2).

The way "b" of reaction Scheme 2 was described in our previous paper.[1] The compound thus obtained (3) transforms under the effect of alkali into the same enamine (2) as prepared via "a" (ν: 1575); and conversely, under the effect of acid the 2 becomes the same as 3 (ν: 1702) obtained via "b". This is undoubted proof of the olefin structure 2 formed in nucleophilic elimination. The difference in the spectra of 2 and 3 is a value characteristic of enamines.[7]

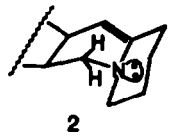
Besides this, 3 obtained via "a" and "b" can be reduced by $NaBH_4$ to the same compound, phenanthro-quinolizidine (1c; 1: R^1, R^2, R^3, R^4, R^5, R^6 = H).

The changes in the conformation of olefin 2 compared with its saturated analogue 1c were evaluated by the use of PMR spectra. For the compounds 1c it was formerly stated on the basis of the Bohlmann bands present in their spectra[8] that in the equilibrium mixture predominantly *trans*-quinolizidine is to be found (1c). By examining a Dreiding model, it can be seen that in this conformation the position of the two protons of 9C is not equivalent as compared with the free electron pair of nitrogen. This is reflected in the different chemical shifts of the two protons, and the high coupling constant (16 Hz) (Table 1, 1c). Similar values were found for cryptopleurine[9] which proves that the conformation of the quinolizidine skeleton is not essentially influenced by the substituents of the phenanthrene skeleton.



1C

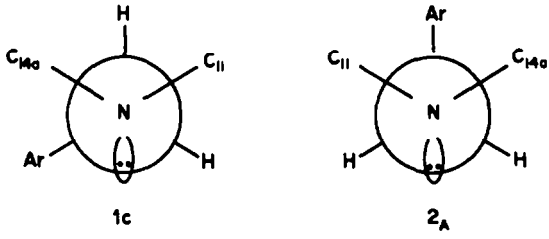
Since the chemical shift of Ar-CH_2-N protons is determined by their position related to the free electron pair of nitrogen[10,11] we can deduce their conformation from the chemical shift. The chemical shift of the two protons of dehydro-quinolizidine (2) analog is equivalent, it appears to be a singlet (Table 1, 2), thus their position



2

is symmetrical both with the free electron pair of nitrogen and with the phenanthrene skeleton. Such a steric position of the 9C protons is possible only when the quinolizidine skeleton has 2_A conformation. As it can be seen the conformation related to the analogous saturated skeleton (1c) has essentially changed. This relation, with the change of the Ar-CH_2-N protons, is well seen when 1c and 2 are plotted in a Newman projection along the 9C–N bond (Fig. 1).

The compound 2 with unsubstituted phenanthrene skeleton is not stable either, it is sensitive to water, air bases and acids. In the air, even in crystalline form, it decomposes. It's a substituted analogue that decomposes more intensively.



1c 2_A

Fig. 1.

EXPERIMENTAL

The IR spectra were taken by UNICAM SP 200, the PMR by JEOL 60 Mc. The m.p. measurements were done with a Koffler block, they are not corrected. Chromatography was carried out upon 10×3 cm Kieselgel-G nach Stahl slides in Benzene:ETOH 50:15 (v/v).

1,10'-*Dehydro-phenantro*(9,10-b)-*quinolizidine* (2)

a. *From immonium* (3) *compound.* 0.5 g 5:10'-dehydro-phenanthro (9,10-b) quinolizidinium ClO_4^{-1} was suspended in 10 ml acetone and carefully mixed with 1 ml 50% KOH and 5 ml water added. The yellow ppt was quickly filtered off, dissolved in acetone and recrystallised by adding (yet more) water and dried over P_2O_5 in N_2 atmosphere, yellow needles m.p.: 139–142°. (Found: C, 88.07; H, 6.9; N, 4.78. ν: 1575. Requires: C, 88.38; H, 6.71; N, 4.90%).

b. *From* 1_A. 0.5 g phenanthro(9-10b)-quinolizidine-1'-ol (isomer A) was heated at 130° in N_2 atmosphere in 25 ml n-amyl alcohol containing 0.5 g K for 72 hr. (The N_2 must be completely free of O_2). Then it was allowed to stand in a N_2 atmosphere. It crystallised in a few hours. It was filtered, then washed with a small

Table 1.

Compound	$\delta_{9\ equ}$	δ_{9ax}	equ–ax
Phenantro-quinolisidine /1c/	4,45	3,56	16
Dehydro-phenantro-quinolisidine /2/	4,63	4,63	-

amount of MeOH several times yielding 0.38 g yellow crystals, m.p. 140–142°. (ν: 1575. Found: C, 88.16; H, 6.82; N, 4.68%). It had no m.p. depression with the compound prepared via "a".

c. *From* 1_B. 0.5 g phenanthro(9,10b)-quinolizidine-1'-ol (isomer B) was heated for over 20 hr under conditions described for 1_A. Isolation as described, m.p. 140–142°C. (ν: 1575. Found: C, 88.20; H, 6.80; N, 4.75%).

Phenanthro(9,10b)-5,10'-dehydroquinolizidinium chloride (3)

Compound 2 (0.5 g) was suspended in 10 ml abs EtOH, then 1 ml 10% EtOH/HCl was added. The crystals dissolved and lost colour. After dissolution, a little ether was added, and colourless crystals formed, m.p. 240° with gradual decomposition. (Found: C, 78.70; H, 6.42; N, 4.73. ν: 1702. Requires: C, 78.37; H, 6.26; N, 4.35%).

Phenanthro(9,10b)-quinolizidine

Compound 3 (0.3 g), suspended in EtOH was reduced in a few minutes with $NaBH_4$, yield: 0.2 g. Recrystallised from benzene, m.p.: 174–175°—in agreement with the lit.[1]

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