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HOMOKETONIZATION OF A 4-ACETOXYHOMOCUNEANE WITH RETENTION OF CONFIGURATION[1)]

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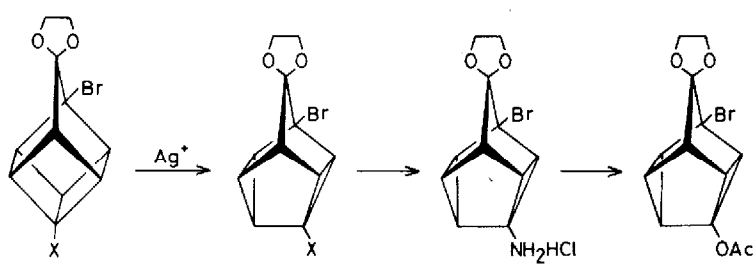
The homoketonization of bridgehead alcohols in highly strained polycyclic systems has received considerable attention in the recent literature. We reported the base-induced cage opening reaction of homocubane and 1,3-bishomocubane alcohols and acetates[2)] which proceeds exclusively with retention of configuration. Cyclobutane and cyclopentane ring opening during base-induced homoketonization reactions in some other cage compounds was also found to occur with predominant retention, viz. for 3,4,5-trichloropentacyclo [4.4.0.0^{2,5}.0^{3,9}.0^{4,8}] decan-2-amine[3)], for 7-phenyltricyclo [3.2.0.0^{2,6}] heptan-7-ol[4)] and for 3,7-dimethyltricyclo [3.3.0.0^{3,7}] octan-1-ol[5)]. In contrast with this, Nickon and coworkers[6)] observed almost exclusive inversion of configuration for the base-induced homoketonization of 1-acetoxynortricyclane 13 and 2-acetoxytriaxane 14 (figure 1). This remarkable difference in the stereochemistry of the ring opening can either be attributed to the special nature of the cyclopropane ring or be determined by the strain features of the polycyclic system in which the cyclopropane ring is constrained. To evaluate these possibilities, we decided to investigate the homoketonization of 1-bromo-4-acetoxypentacyclo [4.3.0.0^{2,4}.0^{3,8}.0^{5,7}] nonan-9-one 7 under basic conditions.

This 4-acetoxyhomocuneane 7 was prepared as outlined in Scheme I, starting from homocubane acid[7)] 1. Reduction of 1 with LAH gave alcohol 2, which could be



1 X = COOH
2 X = CH_2OH

3 X = CH_2OH
4 X = COOH
5 X = CON_3

6

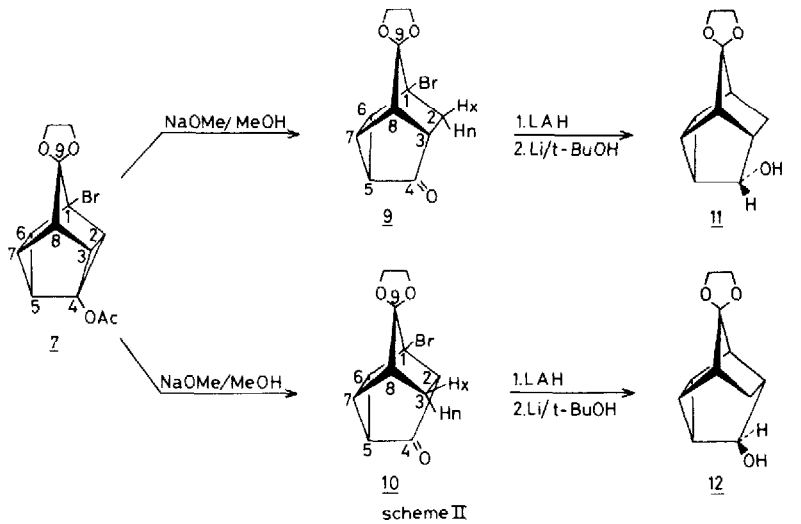
7

scheme I

readily transformed into homocuneane methyl alcohol 3 by $AgNO_3$ in CH_3OH[8)]. Subsequent oxidation with $KMnO_4$ afforded the carboxylic acid 4 in a 50% overall

yield. Attempts to prepare 4 directly by isomerization of 1 with $AgNO_3/CH_3OH$ were unsuccessful. Homocuneane carboxylic acid 4 was converted into the amine hydrochloride 6 via a Curtius rearrangement of the carbonylazide 5 (55% overall yield). Deamination of 6 with $NaNO_2$ in acetic acid then gave 4-acetoxyhomocuneane 7 in a 64% yield.

Homocuneane acetate 7 turned out to be extremely base labile. Upon treatment with NaOMe in MeOH at room temperature an instantaneous reaction took place. After work up, a crystalline material was obtained in almost quantitative yield. Although GLC and TLC suggested a single product, the melting range (105-130°) was indicative of a mixture. A separation could be accomplished by column chromatography (silicagel, toluene/chloroform 1:5) as well as by repeated crystallization from CCl_4 to give two compounds: m.p. 129-131° and m.p. 155-156°, to which the structures 9 and 10 could be assigned[9] respectively, on the basis of spectral data (Scheme II).



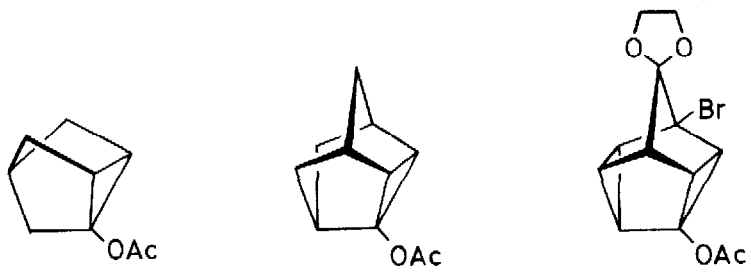
scheme II

The IR spectrum of 9 and 10 showed a cyclopropane absorption at 3070 cm^{-1} and a carbonyl absorption at 1730 cm^{-1}, characteristic for a five-membered ring ketone. The NMR spectrum of 9 (C_6D_6) displayed the expected assymmetrical multiplet for the ethylene ketal protons at δ 3.2-4.0 and a complicated pattern for the protons H_3, H_5, H_6, H_7, H_8 and the exo-proton H_x. A doublet (one half of an AB pattern) for one proton was observed at δ 1.78 which was assigned to the endo-proton H_n for the following reasons: *(i)* the dihedral angle between H_n and H_3 is about 90° as indicated by molecular models, therefore, the coupling between these protons will be close to zero and consequently the observed coupling (1 1Hz) must be due to coupling with H_x, *(ii)* the anisotropic deshielding effect of the ethylene ketal function[2] on H_x and the shielding effect of the carbonyl function on H_n will both result in a higher field absorption for the endo-proton H_n as compared with H_x, *(iii)* the large shift gradient for this doublet observed

by using the upfield shift reagent $Pr(fod)_3$ can only be reconciled by assigning this absorption to the H_n proton. A large shift was also observed for the protons H_3 and H_5, because of coordination of $Pr(fod)_3$ with the carbonyl function. Shift reagent experiments together with spin-spin decoupling techniques revealed multiplets for H_3,H_5 and H_x.

The NMR spectrum of 10 (C_6D_6) exhibited an asymmetrical multiplet for the ketal protons at δ 3.2-4.0, a complex pattern for H_2,H_5,H_6,H_7,H_8 and H_x and a doublet (half of an AB pattern, $JH_xH_n \sim 11Hz$) for H_n at δ 1.2 (the coupling of H_n with H_2 and H_8 is negligible since the dihedral angles are about 90°). With Eu $(dpm)_3$ a large downfield shift for H_2 and H_5 was observed. H_2 appeared as a sharp doublet due to coupling with H_x. These data are only consistent with structure 10. It should be noted, that the differentiation between the structures 9 and 10 is based mainly on the multiplicity of the signal for H_3 in 9 and that of H_2 in 10, and on the difference in chemical shift of H_n in 9 and 10 due to a deshielding effect of the bridgehead bromine atom on H_n in 9. The relationship between 9 and 10 was established unambiguously by reduction with LAH and subsequent reductive debromination with Li in t-BuOH. In both cases the same mixture of enantiomers 11 and 12 was obtained (Scheme II).

After having elucidated the structures 9 and 10, the stereochemistry of the cage opening could be studied. Treatment of acetate 7 with NaOMe in MeOD gave a mixture of the monodeuterated ketones 9 and 10. The NMR spectrum of deuterated 9 (C_6D_6) showed unchanged signals for the ketal protons and protons H_3,H_5,H_6,H_7 and H_8, a doublet for H_x at δ 2.52 ($JH_xH_3 \sim 8Hz$), and the absence of the AB pattern for H_n at δ 1.78. Similarly, the spectrum of 10 revealed that H_n was replaced by D. This labeling experiment convincingly shows that the base-induced homoketonization of 4-acetoxyhomocuneane 7 is a stereospecific process proceeding with retention of configuration [10] (> 96%). Strikingly, this stereochemical result is completely opposite to the inversion of configuration observed by Nickon and coworkers[6] for the base-induced cyclopropanol ring opening in 1-acetoxynortricyclane 13 and 4-acetoxytriaxane 14 (figure 1). The retention of configuration for the homoketonization of 4-acetoxyhomocuneane 7, as mentioned



13 14 7

figure 1

above, rather conforms to the pattern of stereochemical results observed for the

cleavage of cyclobutanols[2,4] and cyclopentanol[5] incorporated in a highly strained polycyclic system. Clearly, our results show that inversion of configuration is not a general feature for the base-induced ring opening of cyclopropanols constrained in a polycyclic structure [11]. Furthermore, we suggest that the stereochemical course of the base-induced homoketonization in general, will be predominantly governed by the total strain of the polycyclic system and the release of strain during the process of ring opening. During the base-induced cleavage of a bridgehead alcohol in extremely highly strained polycyclic systems, a carbanion is created that is hardly shielded by the carbonyl function because the conformational strain forces it apart at considerable distance. The stereochemical consequence is clearly retention: the uninverted carbanion is immediately protonated since it is surrounded by favourably disposed solvent molecules on its open face. In less strained systems, such as nortricyclane and triaxane, considerable shielding of the developing carbanion may occur as the conformational strain in the products is not sufficiently large to separate the carbanion and carbonyl function completely. Substantial homoconjugative stabilization of the carbanion is possible and protonation takes place from the exo side which leads to inversion.

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9. Recently, T. Sasaki and coworkers reported on the ring opening of some homocuneane urethane derivatives. However, no information on the stereochemistry of this reaction was given; T. Sasaki, S. Eguchi, F. Hibi and O. Hiroaki, J. Org. Chem., 40, 845 (1975).
10. It may be argued that the stereochemistry of cage opening may be influenced by the presence of the ethylene ketal function. However, in the homocubane and 1,3-bishomocubane series, we demonstrated that the ketal function had no effect at all on the stereochemistry of homoketonization[2] and from molecular models it is apparant that the spatial arrangement of the ketal function in the homocuneane and homocubane systems is comparable.
11. We recently found that the acid-induced cleavage of the 1-acetoxyhomocuneane 7 proceeds with exclusive retention of configuration. This result conforms to the general pattern of acid-induced homoketonization; see A. Nickon, J.J. Frank, D.F. Covey, Y-i Lin, J. Amer. Chem. Soc., 96, 7574 (1974).