CHEMISTRY OF STRAINED POLYCYCLIC COMPOUNDS—V^1

THE STEREOSELECTIVE CATIONIC CAGE EXPANSION REACTION
OF 4-HOMOCUBANE CARBINOLS TO 1,3-BISHOMOCUBANE
BRIDGEHEAD ALCOHOLS

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Abstract—The cationic rearrangement of four homocubane bridgehead carbinols viz dimethyl 4-(1-
 bromopentacyclo[4.3.0.0^2,5.0^3,8.0^4,7]nonyl-9-one ethylene ketal) carbinol 2, diphenyl 4-(1-bromopenta-
cyclo[4.3.0.0^2,5.0^3,8.0^4,7]nonyl-9-one ethylene ketal) carbinol 3, 4-(1-bromopentacyclo[4.3.0.0^2,5.0^3,8.0^4,7]
nonyl-9-one ethylene ketal) carbinol 4 and 4-(1-bromopentacyclo[4.3.0.0^2,5.0^3,8.0^4,7]nonyl) carbinol 16,
have been studied under various conditions.

Exclusive migration of the C_4—C_7 (or the equivalent C_3—C_4 bond) in the homocubane skeleton
was observed leading to 1,3-bishomocubane bridgehead alcohols. Relief of cage constraint governs the
selective course of these cage expansions.

Anions adjacent to a bridgehead position in strained polycyclic systems can induce stereospecific re-
arrangements of these compounds, as exemplified by the homoketonization of a homocubane bridge-
head alcohol. In order to study this interesting rearrangement in more detail, particularly the in-
fluence of ring strain, a number of cage alcohols was required, which show a diversity in strain
energy.

In a previous paper we described the synthesis of cubane and homocubane alcohols. This paper
deals with the preparation of 1,3-bishomocubane bridgehead alcohols by a stereospecific cationic
cage expansion reaction of homocubane bridgehead carbinols.

The required carbinols, i.e. 2, 3, 4 and 16 were easily accessible from the homocubane-4-carboxy-
ic acid 14 or its ester 1^4 (Schemes I and II).

The cationic rearrangement of the carbinols 2, 3, 4 and 16 was studied under a variety of conditions (Schemes I and II). Upon treatment with HCl aq dimethylcarbinol 2 gave a mixture of two main products 5 and 7. Alcohol 7 was obtained in 57% yield and characterized by an OH absorption at 3400 cm^{-1}, a C=O absorption at 1775 cm^{-1} in the IR spectrum and by two singlets for the Me groups at \( \delta \) 0.78 and \( \delta \) 0.92 ppm in the NMR spectrum. These NMR signals can only be reconciled with structure 7 since only migration of the C_4—C_7 bond or the equivalent C_3—C_4 bond in 2 will lead to a bishomocubane derivative in which the two Me groups are non-equivalent. The alternative mode of 1,2-bond shift, viz, of the central C_4—C_5 bond, would have given a 1,4-bishomocubane in which the two Me groups are identical.

The NMR spectrum of chloride 5 (yield 27%) also displays two singlets for the Me groups at \( \delta \) 0.75 and \( \delta \) 0.94, and in addition a symmetrical multiplet for the ethylene ketal function^* at \( \delta \) 3.80-4.40, a multiplet at \( \delta \) 3.00-3.25 for the cage protons at C_2,3,4, and a multiplet at \( \delta \) 2.40-2.65 ppm for the cage protons at C_5 and C_6. Treatment of 2 with HBr aq similarly gave dibromide 6 and alcohol 7. Under these conditions ketalized alcohol 8 could not be obtained. Apparently hydrolysis of the ketal function takes place readily, presumably, because 8 is quite soluble in aqueous acid. The halides 5 and 6, on the other hand, are almost insoluble in aqueous acid, and consequently, hydrolysis to the corresponding haloketones will not take place that easy. However, ketal alcohol 8 could be obtained in 40% yield by treatment of the carbinol 2 with SOCl_2. This reaction leads to a mixture of chloride 5 and ketal alcohol 8. Of course, ketalization of ketone alcohol 7 with HOCH_2CH_2OH/TosOH also provided ketal alcohol 8. Treatment of 2 with PBr_3 gave a mixture of dibromide 6 and alcohol 8 (contaminated with some of its phosphite ester). Interestingly, neither the reaction of 2 with SOCl_2 nor that with PBr_3 leads to simple halide formation, only rearranged products were obtained. Even the application of these reagents in the presence of pyridine did not change the reaction course. An attempt to prepare unrearranged 4-homocubane

^*When a symmetrical absorption is observed, it does not necessarily imply that the ketal containing compound has a plane of symmetry.\(^2\)
isopropylbromide by treatment of 2 with Ph3P/Br2
in DMF* only resulted in the isolation of rearranged
formate 9 in 68% yield. The latter product gave
upon transesterification ketal alcohol 8 in quanti-
tative yield.

Although mass spectral data can not differentiate
between 1.3 and 1.4-bishomocubanes, these types
of cage compounds do show a characteristic crack-
ing pattern, viz cleavage of the cage system in half.7
Indeed intense peaks were observed at m/e 128, 130
(C7H9Cl+) for chloride 5, at m/e 172, 174 (C7H9Br+)
for bromide 6 and at m/e 110 (C7H10O+) for alcohol
8.

Carbinol 4, when treated with SOCl2, afforded
chloride 10 and alcohol 11 in 30% and 45% yield,

*Triphenylphosphine dibromide in DMF is known for
its ability to give bromination without rearrangement.6

Scheme 1
respectively (Scheme I). In contrast to dimethylcarbinol 2, carbinol 4 could be converted into un-rearranged homocubane methylchloride 12 or methylbromide 13 by treatment with SOCl₂ in the presence of pyridine or by treatment with PBr₃ in ether at −25°C, respectively. In both cases only a small amount of rearranged products was isolated. It should be noted that 12 and 13 could be obtained in high yields, free from rearranged products, by a S₄N₂ displacement reaction of the tosylate of 4 with LiCl or LiBr in acetone.

Diphenylcarbinol 3 showed a different behaviour. Upon treatment with HCl aq or SOCl₂, no bridgehead bishomocubane alcohol was formed, but instead, a high melting solid (m.p. 281–288°C) was isolated which was insoluble in most organic solvents. Thusfar, no structure could be assigned to this compound on account of the available spectroscopic and chemical data.

Carbinol 16 gave upon treatment with SOCl₂ a mixture of chloride 17 and alcohol 19 in 30% and 67% yield, respectively (Scheme II). The NMR spectrum of 17 as well as of 19 displays two unsymmetrical doublets for the methylene protons at C₆ and at C₁₀, which is unambiguous evidence for the asymmetric structure of the proposed bishomocubane products. The mass spectra of 17 and 19 exhibit intense peaks arising from cleavage of the bishomocubane skeleton in half, at m/e 100, 102 (C₅H₅Cl⁺) and 144, 146 (C₅H₅Br⁺) for the chloride 17, and at m/e 82 (C₅H₄O⁺) and 65 (C₅H₄Br⁺) for the alcohol 19. The carbinol 16 gave, upon treatment with PBr₃, a mixture of dibromide 18 and alcohol 19 (together with some of its phosphite ester). The same dibromide 18 could be prepared from 1,3-bishomocubane dione 20 by a Wolff-Kishner reduction, and hence confirming the proposed structure.

In conclusion it may be pointed out that the cationic rearrangement of homocubane carbinols provides an attractive route for the synthesis of bridgehead 1,3-bishomocubane alcohols. These compounds are not easily accessible by other routes. The driving force in this stereospecific cationic rearrangement most likely is relief of ring strain leading to the 1,3-bishomocubane cage system by exclusive migration of the C₄—C₇ bond (or the equivalent C₂—C₇ bond) in the homocubane skeleton. 1,4-Bishomocubane derivatives arising from a 1,2 shift of the central C₁—C₇ bond were not observed. The present results are in line with the previous observation of exclusive cleavage of the C₄—C₇ bond (or the equivalent C₃—C₇ bond) during the homoketonization reaction of a bridgehead homocubane alcohol with an OH at the 4-position.² Apparently in both cases relief of cage strain is higher by cleavage of the C₄—C₇ (or C₃—C₄) bond than of the C₆—C₈ bond. This energy difference is responsible for the high selective bond migration.
Methyl 1-bromopentacyclo[4.3.0.0^2,5.0^3.0^7]nonan-9-one ethylene ketal 4-carboxylate (I)
Carboxylic acid 1A, prepared as described by Key, was esterified with CH\(_2\)\(_2\)\(_2\)N\(_2\) to give 1 (97%), m.p. 107-109\(^\circ\)C.

**EXPERIMENTAL**

IR spectra were taken on a Perkin-Elmer 125 grating spectrometer. NMR spectra were recorded on a Varian A60 spectrometer, using TMS as internal standard. All m.ps are uncorrected and determined on a Kofler hot stage. Elemental analyses were carried out in duplicate (their average values are reported), in the microanalytical department of the University at Groningen under supervision of Mr. W. M. Hazenberg.

**6,6-Dimethyl-9-bromopentacyclo[5.3.0.0^3,6,0^8.0^9]deca-1,8-diene 9-one ethylene ketal 5-formate 9**

To a stirred ice-cooled soln of carbinol 2 (0-2 g, 0-6 mmole) in DMF (3 ml) was added triphenylphosphine (0-2 g, 0-7 mmole). Then bromine (0-12 g, 0-7 mmole) was added at such a rate that the reaction temp could be kept below 55\(^\circ\)C. After stirring at room temp for 18 hr, the mixture was diluted with water and extracted with ether. The ether layer was dried (MgSO\(_4\)) and concentrated to give crude 6 (0-2 g, 0-7 mmole). Then bromine (0-18 g, 1-1 mmole) in HC\(_2\)\(_2\)aq (5 ml) was stirred overnight. The mixture was added at such a rate that the reaction temp could be kept below 55\(^\circ\)C. After stirring at room temp for 18 hr, the mixture was poured into ice-water and extracted with ether. The extracts were washed with Na\(_2\)CO\(_3\) aq (5%) and dried (MgSO\(_4\)). Solvent was evaporated yielding an oil which was chromatographed over silica. Elution with benzene furnished formate 9 (0-15 g, 27%). Recrystallization from hexane furnished 9 (0-94 g, 27%). IR \(_{\text{max}}\) 1730 (C=O), 1175 (ester) cm\(^{-1}\); NMR (\(\text{CDCl}_3\)) \(\delta\) 3-75-4-40 (sym.m, 4H, ketal group), 3-00-3-35 (4H), 2-35-2-75 (m, 2H, protons at C\(_2\) and C\(_3\)), 0-93 (s, 3H, methyl), 0-75 (s, 3H, Me); m/e 376 (M\(^+\), 28%), 173 (C\(_2\)-H\(_2\)Br), 137 (C\(_2\)-H\(_2\)Br). (Found: C, 54-10; H, 4-34; Br, 42-49%; Calc. for C\(_{14}\)H\(_{16}\)Br\(_2\)O\(_2\): C, 54-74; H, 5-33; Br, 45-59%.) Further elution with ether gave alcohol 7 (70%).

**Rearrangement of 2 with SOCl\(_2\)**

A soln of carbinol 2 (1-0 g, 3-2 mmole) in SO\(_2\)Cl\(_2\) (15 ml) was stirred at room temp for 2 days. Then the mixture was poured into ice-water and extracted with ether. The extracts were washed with Na\(_2\)CO\(_3\) aq (5%) and dried (MgSO\(_4\)). Solvent was evaporated yielding a mixture of chloride 5 and alcohol 6, which was separated by chromatography over silica. Elution with benzene afforded the chloride 5 (0-25 g, 23%). Further elution with ether gave alcohol 6 as an oil. Crystallization from hexane afforded pure alcohol 6 (0-7 mmole, m.p. 88-5-89-5\(^\circ\)C (after drying at 70/12 mm for 24 hr); IR \(_{\text{max}}\) 3310 (OH), 1717 (C=O), 1175 (ester) cm\(^{-1}\); NMR (\(\text{CDCl}_3\)) \(\delta\) 4-05-4-38 (m, 2H, protons at C\(_2\) and C\(_3\)), 1-87 (s, 1H, OH), 1-57 (s, 1H, OH), 1-10 (s, 3H, Me); m/e 350 (M\(^+\)), 254 (M\(^+\) - C\(_2\)-H\(_2\)OH, 1Br). (Found: C, 56-52; H, 4-63; Br, 18-27; Calc. for C\(_{14}\)H\(_{16}\)Br\(_2\)O: C, 56-91; H, 4-84; Br, 18-27%).

**Diphényl 4-(1-bromopentacyclo[4.3.0.0^2,5.0^3.0^7]nonan-9-one ethylene ketal carbinol (3)**
This was prepared as described above using PhMgBr instead of MeMgI. Ester 1 gave 3 in 87% yield, m.p. 165-2-166-5\(^\circ\)C (recrystallized from hexane); IR \(_{\text{max}}\) 1730 (C=O), 1175 (ester) cm\(^{-1}\); NMR (\(\text{CDCl}_3\)) \(\delta\) 2-35-3-00 (m, 5H, 1H proton at C\(_4\)), 3-7-4-40 (sym.m, 4H, ketal group), 3-05-3-45 (m, 2H, phenyl), 3-00-3-50 (m, 5H, 1H proton at C\(_3\)), UV (EtOH) \(\lambda_{\text{max}}\) in nm (e) 251 (496); 258 (564); 264 (449); (Found: C, 76-52; H, 4-63; Br, 18-27; Calc. for C\(_{14}\)H\(_{16}\)Br\(_2\)O: C, 76-91; H, 4-84; Br, 18-27%).

**Rearrangement of 2 with PBr\(_3\)**
The same procedure as in the rearrangement of 2 with SO\(_2\)Cl\(_2\) was used, giving a mixture of dibromide 6 and alcohol 8 (together with its phosphte ester) which was separated by chromatography over silica. Elution with benzene gave pure dibromide 6 (14%). Further elution with ether gave alcohol 8 (30%) contaminated with some of its phosphte ester.
temp for 16 hr. The SOCl₂ was removed in vacuo, the residue diluted with water and ether extracted. The ether layer was dried (MgSO₄) and concentrated to give a dark brown oil which was chromatographed over silica. Elution with benzene afforded ketol 10 (0.38 g, 30%). Recrystallization from hexane and subsequent sublimation in vacuo gave a pure sample, m.p. 72-76°; IR νₑₑₑₑ 1310, 1050, 980 cm⁻¹; NMR (CDCl₃) δ 3.74-4.37 (symm., 4H, ketol group), 2.8-3.3 (m, 5H), 2.05-2.5 (m, 1H, proton at C₁), 1.96 (AB quartet, J = 2 Hz, 2H, protons at C₂); m/e 303 (M⁺, 1Br), 265 (M⁺, 1Br, C₂O) (Found: C, 41.41; H, 3.58; Br, 45.44; Calc. for C₁₀H₁₃BrO₂: C, 41.41; H, 3.48; Br, 45.93%).

Further elution with benzene/ether gave ketal 11 (0.45 g, 45%). Crystallization from diethylene glycol (70 ml) and KOH (4.5 g) were added and the soln extracted with ether. The extracts were dried (MgSO₄) and the solvent evaporated to give chloride 12 (0.15 g, 70%) as a solid which yielded on standing, m.p. 73.5-84.5° (hexane); IR νₑₑₑₑ 3250 (OH) cm⁻¹; NMR (CDCl₃) δ 3.64-4.37 (symm., 4H, ketal group), 3.64 (s, 2H, —CH₂—Br), 3.4-3.6 (m, 5H), 2.7-3.1 (m, 1H, proton at C₁).

(A) From carbinol 4. A soln of 4 (0.4 g, 1.3 mmole) was added dropwise to a soln of 2 (0.2 g, 0.7 mmole) in pyridine (1.0 g, 13 mmole). After being stirred for 8 hr at 75°, the mixture was poured onto crushed ice and extracted with ether. The ether phase was dried (MgSO₄) and concentrated to give chloride 12 (0.14 g, 30%). Crystallization from hexane gave an analytically pure sample, m.p. 114-120°; IR νₑₑₑₑ 3350 (OH) cm⁻¹; NMR (CDCl₃) δ 3.75-4.35 (symm., 4H, ketal group), 2.65-3.30 (m, 5H), 2.57 (s, 1H, OH), 2.27-2.45 (m, 1H, proton at C₁), 1.73 (AB quartet, 2H, protons at C₆); m/e 285 (M⁺, 1Br), 196 (M⁺, 1Br, C₂O) (Found: C, 48.81; H, 4.20; Br, 32.18; Cl, 14.39; Calc. for C₁₄H₁₄BrCl: C, 48.90; H, 4.10; Br, 32.54; Cl, 14.43%).

Further elution with ether gave alcohol 19 (67%) as an oil, which solidified on standing, m.p. 73.5-84.5° (hexane); IR νₑₑₑₑ 3250 (OH) cm⁻¹; NMR (CDCl₃) δ 2.93-3.25 (m, 4H), 2.5-2.9 (m, 2H, protons at C₁ and C₂), 1.97 (complex AB pattern, 4H, protons at C₆ and C₁₀; m/e 145 (C₆H₁₄Br), 100 (C₂H₄Cl²). (Found: C, 48.81; H, 4.20; Br, 32.18; Cl, 14.39; Calc. for C₁₄H₁₄BrCl: C, 48.90; H, 4.10; Br, 32.54; Cl, 14.43%).

(A) From the tosylate of 4. A mixture of the tosylate of 4 (1.5 g, 13 mmole) was added slowly to a slurry of LAH in ether. After cooling to room temp, water was added and the soln extracted with ether. The extracts were dried (MgSO₄) and concentrated to give a yield of the methylbromide 13 (0.45 g, 45%). Recrystallization from hexane gave an analytically pure sample, m.p. 114-120°; IR νₑₑₑₑ 3350 (OH) cm⁻¹; NMR (CDCl₃) δ 3.75-4.35 (symm., 4H, ketal group), 2.65-3.30 (m, 5H), 2.57 (s, 1H, OH), 2.27-2.45 (m, 1H, proton at C₁), 1.73 (AB quartet, 2H, protons at C₆); m/e 285 (M⁺, 1Br), 196 (M⁺, 1Br, C₂O) (Found: C, 48.81; H, 4.20; Br, 32.18; Cl, 14.39; Calc. for C₁₄H₁₄BrCl: C, 48.90; H, 4.10; Br, 32.54; Cl, 14.43%).

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REFERENCES
