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CHEMISTRY OF STRAINED POLYCYCLIC COMPOUNDS—V

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[4.3.0.0².5.0³.8.0⁴.7]nonyl-9-one ethylene ketal) carbinol 2, diphenyl 4-(1-bromopentacyclo[4.3.0.0².5.0³.8.0⁴.7]nonyl-9-one ethylene ketal) carbinol 3, 4-(1-bromopentacyclo[4.3.0.0².5.0³.8.0⁴.7]nonyl-9-one ethylene ketal) carbinol 4 and 4-(1-bromopentacyclo[4.3.0.0².5.0³.8.0⁴.7]nonyl) carbinol 16, has been studied under various conditions. Exclusive migration of the C₄—C₇ (or the equivalent C₃—C₄ 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 rearrangements of these compounds, as exemplified by the homoketonization of a homocubane bridgehead alcohol. In order to study this interesting rearrangement in more detail, particularly the influence 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-carboxylic acid 14 or its ester 14 (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 δ 0.78 and δ 0.92 ppm in the NMR spectrum. These NMR signals can only be reconciled with structure 7 since only migration of the C₄—C₇ bond or the equivalent C₃—C₄ 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 C₄—C₅ 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 δ 0.75 and δ 0.94, and in addition a symmetrical multiplet for the ethylene ketal function* at δ 3.80-4.40, a multiplet at δ 3.00-3.25 for the cage protons at C₂, C₃, C₅, a multiplet at δ 3.00-3.25 for the cage protons at C₂, C₃, C₅, a multiplet at δ 3.00-3.25 for the cage protons at C₂, C₃, C₅, a multiplet at δ 3.00-3.25 for the cage protons at C₂, C₃, C₅, a multiplet at δ 3.00-3.25 for the cage protons at C₂, C₃, C₅. 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 SOCl₂. This reaction leads to a mixture of chloride 5 and ketal alcohol 8. Of course, ketalization of ketone alcohol 7 with HOCH₂CH₂OH/TosOH also provided ketal alcohol 8. Treatment of 2 with PBr₃ gave a mixture of dibromide 6 and alcohol 8 (contaminated with some of its phosphite ester). Interestingly, neither the reaction of 2 with SOCl₂ nor that with PBr₃ 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.
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 quantitative yield.

Although mass spectral data cannot differentiate between 1,3 and 1,4-bishomocubanes, these types of cage compounds do show a characteristic cracking pattern, viz cleavage of the cage system in half. 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.

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*Triphenylphosphine dibromide in DMF is known for its ability to give bromination without rearrangement."
respectively (Scheme I). In contrast to dimethylcarbinol 2, carbinol 4 could be converted into un-rearranged homocubane methyl chloride 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 Sₙ₂ 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, 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⁺-Br) 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 C₅—C₆ bond) in the homocubane skeleton. 1,4-Bishomocubane derivatives arising from a 1,2 shift of the central C₄—C₅ bond were not observed. The present results are in line with the previous observation of exclusive cleavage of the C₄—C₁₅ bond (or the equivalent C₅—C₁₆ 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 C₅—C₆) bond than of the C₄—C₅ bond. This energy difference is responsible for the high selective bond migration.
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 Koffler 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.

Methyl 1-bromopentacyclo[4.3.0.02,6.04.9]nonan-9-one ethylene ketal 4-carboxylate (1)

Carboxylic acid 14, prepared as described by Key et al., was esterified with CH₂N₂ to give 1 (97%), m.p. 107-109° (lit.: m.p. 106-108°).

Dimethyl 4-(1-bromopentacyclo[4.3.0.02,6.04.9]nonan-9-one ethylene ketal) carbinal (2)

A solution of 1 (0.5 g, 1.6 mmole) in anhyd ether (25 ml) was added to a solution of MeMgI in ether. After stirring overnight, the mixture was diluted with water and extracted with ether. The ether layer was dried (MgSO₄) and concentrated to give crude 2 (0.5 g, 95%). Recrystallization from hexane gave a pure sample: m.p. 114-115°; IR νmax 3500, 3440 (O—H) cm⁻¹; NMR (CDCl₃): δ 3.75-4.38 (sym.m, 4H, ketal group), 3.3-3.5 (3H, 5H), 2.55-2.85 (m, 1H, proton at C₈), 1.27 (s, 1H, OH), 1.70 (s, 6H, Me); m/e 254 (M—CH₂OH, 1Br). (Found: C, 54-10; H, 5-61; Br, 25-70; Calc. for C₂H₃BrO₂C: C, 53-69; H, 5-47; Br, 25-52%).

Diphenyl 4-(1-bromopentacyclo[4.3.0.02,6.04.9]nonan-9-one ethylene ketal) carbinal (3)

This was prepared as described above using PhMgBr instead of MeMgI. Ester 1 gave 3 in 87% yield, m.p. 162.5-164.5° (recrystallized from hexane); IR νmax 3600 (O—H), 1320 cm⁻¹; NMR (CDCl₃): δ 3.00-3.35 (m, 4H), 2.35-2.75 (m, 2H, protons at C₈ and C₇), 0.93 (s, 3H, methyl), 0.78 (s, 3H, Me); m/e 376 (M⁺, 2Br), 173 (C₂H₅Br). (Found: C, 45-09; H, 4-34; Br, 42-14; Calc. for C₁₇H₂₃BrO₄C: C, 44-71; H, 4-29; Br, 42-49%). Further elution with ether gave alcohol 7 (70%).

A rearrangement of 2 with SOCl₂. A solution of carbinal 2 (1-0 g, 3-2 mmole) in SOCl₂ (15 ml) was stirred at room temp for 2 days. Then the mixture was poured into water and extracted with ether. The extracts were washed with NaHCO₃ aq (5%) and dried (MgSO₄). Solvent was evaporated giving dichromide 8 (40%), m.p. 88.5-89.5° (after drying at 70°/12 mm for 24 hr); IR νmax 3320 (OH), 1320 cm⁻¹; NMR (CDCl₃): δ 3.75-4.38 (sym.m, 4H, ketal group), 3.40-3.75 (2H, 5H), 2.15-2.45 (m, 1H, proton at C₈), UV (EtOH) λmax in nm (e) 251 (496); 258 (564); 264 (449). (Found: C, 55-52; H, 4-63; Br, 18-27; Calc. for C₁₇H₂₃BrO₂C: C, 55-91; H, 4-84; Br, 18-27%).

Further elution with ether gave carbinal 9 as an oil. Crystallization from hexane afforded pure alcohol 8 (0.4 g, 40%), m.p. 88.5-89.5° (after drying at 70°/12 mm for 24 hr); IR νmax 3320 (OH), 1320 cm⁻¹; NMR (CDCl₃): δ 3.75-4.40 (sym.m, 4H, ketal group), 3.40-3.75 (2H, 5H), 2.15-2.45 (m, 1H, proton at C₈), 1-60 (1H, OH), 0-87 (s, 3H, Me), 0-70 (s, 3H, methyl); m/e 313 (M⁺, 1Br), 110 (C₈H₇O). (Found: C, 53-74; H, 5-33; Br, 25-55; Calc. for C₁₇H₂₃BrO₂C: C, 53-69; H, 5-47; Br, 25-59%).

A rearrangement of 2 with PBr₃. The same procedure as in the rearrangement of 2 with SOCl₂ was used, giving a mixture of dibromide 6 and alcohol 8 (together with its phosphite ester) which was separated by chromatography over silica. Elution with benzene afforded the chloridine 5 (0-25 g, 23%). Further elution with ether gave alcohol 8 as an oil. Crystallization from hexane afforded pure alcohol 8 (0-4 g, 40%), m.p. 88.5-89.5° (after drying at 70°/12 mm for 24 hr); IR νmax 3320 (OH), 1320 cm⁻¹; NMR (CDCl₃): δ 3.75-4.40 (sym.m, 4H, ketal group), 3.40-3.75 (2H, 5H), 2.15-2.45 (m, 1H, proton at C₈), 1-60 (1H, OH), 0-87 (s, 3H, Me), 0-70 (s, 3H, methyl); m/e 313 (M⁺, 1Br), 110 (C₈H₇O). (Found: C, 53-74; H, 5-33; Br, 25-55; Calc. for C₁₇H₂₃BrO₂C: C, 53-69; H, 5-47; Br, 25-59%).

Further elution with ether gave alcohol 8 (30%) contaminated with some of its phosphite ester.

6,6-Dimethyl-9-bromopentacyclo[5.3.0.0²,9.05,13.07,16.06,14]dodeca-10-one ethylene ketal 5-formate (9)

To a stirred ice-cooled solution of carbinal 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 5°. After stirring at room temp for 18 hr, the mixture was diluted with water and extracted with ether. The ether layer was dried (MgSO₄) and concentrated to give an oil which was chromatographed over silica. Elution with benzene furnished formate 9 (0-15 g, 68%).

A rearrangement of 2 with HCl. A slurry of 2 (0.3 g, 1 mmole) in HCl aq (5 ml) was stirred overnight. The ether solvent was washed with NaHCO₃ aq (5%) and dried (MgSO₄). Solvent was evaporated yielding an oil which was dissolved in benzene and chromatographed over silica. Elution with benzene furnished 9 (0.09 g, 27%).

Recrystallization from hexane and subsequent sublimation (100°/12 mm) gave a pure sample, m.p. 117-122°; IR νmax 3450 (O—H) cm⁻¹; NMR (CDCl₃): δ 3.75-4.40 (sym.m, 4H, ketal group), 3.00-3.25 (m, 4H), 2.40-2.65 (m, 2H, protons at C₈ and C₇), 0.94 (s, 3H, Me), 0.75 (s, 3H, Me); m/e 331 (M⁺, 1Br), 1310, 1045, 990 cm⁻¹; NMR (CDCl₃): δ 8.00-8.40 (sym.m, 4H, ketal group), 3.00-3.25 (m, 4H), 2.40-2.65 (m, 2H, protons at C₈ and C₇), 0.94 (s, 3H, Me), 0.75 (s, 3H, Me); m/e 331 (M⁺, 1Br), 128 (C₈H₇Cl). (Found: C, 50-61; H, 4-96; Br, 24-17; Calc. for C₁₇H₂₃BrO₂C: C, 50-70; H, 4-86; Br, 24-10; Cl, 10-69%).
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 ketal 10 (0.38 g, 30%). Recrystallization from hexane and subsequent sublimation in vacuo gave a pure sample, m.p. 72-76°; IR νmax 3130, 1050, 980 cm⁻¹; NMR (CDCl₃) δ 3.74-4.37 (sym.m, 4H, ketal group), 2.8-3.3 (m, 5H), 2.15-2.5 (m, 1H, proton at C₁0), 1.96 (AB quartet, J = 10 Hz, 2H, protons at C₉); m/e 303 (M⁺, 1 Br), 255 (M⁺, 1 Br). (Found: C, 52.07; H, 4.32; Br, 31.37; Calc. for C₁₆H₁₁BrO₃: C, 51.79; H, 4.35; Br, 31.33%).

4-(1-Bromopentacyclo[4,3,0.0².0⁶.0³] nonyl) carbinol 16

A soln of ester 15 (1.4 g, 5.5 mmole) in anhyd ether (20 ml) was added gradually to a slurry of LAH in ether. After stirring overnight, the mixture was diluted with water and extracted with ether. The ether layer was dried (MgSO₄) and concentrated to give crude carbinol 16 (1.2g, 95%). Crystalization from pentane gave an analytically pure sample, m.p. 44-46°; IR νmax 3350 (OH) cm⁻¹; NMR (CDCl₃) δ 3.64 (s, 2H, —CH₂O—), 2.9-3.4 (m, 4H, 6H), 2.14 (d, J = 1-5 Hz, 2H, protons at C₈); 1.43 (d, 1H, OH) m/e 196 (M⁺—CH₂OH). (Found: C, 52.80; H, 4.91; Br, 35.12; Calc. for C₁₁H₁₅BrO: C, 52.89; H, 4.88; Br, 35.19%).

Rearrangement of 16 with SOCl₂

The same procedure as for the rearrangement of 4 with SOCl₂ was used, giving a mixture of chloride 17 and alcohol 19 which was separated by chromatography over silica. Elution with hexane furnished 17 (30%). Crystalization from EtOH and subsequent sublimation (70°C/12 mm) gave an analytically pure sample, m.p. 54-64°; IR νmax 1090, 855 cm⁻¹; NMR (CDCl₃) δ 2.9-3.3 (m, 4H, 6H), 2.5-2.9 (m, 2H, protons at C₈ and C₉), 1.97 (complex AB pattern, 4H, protons at C₈ and C₉); m/e 145 (C₉H₁₅Br), 100 (C₆H₁₁Cl²). (Found: C, 48.81; H, 4.20; Br, 32.18; Cl, 14.39; Calc. for C₁₁H₁₅BrCl²: C, 48.90; H, 4.10; Br, 32.54; Cl, 14.43%). Further elution with ether gave 19 (67%) as an oil, which solidified on standing, m.p. 73.5-84.5° (hexane); IR νmax 3250 (OH) cm⁻¹; NMR (CDCl₃) δ 2.35-2.25 (m, 6H, 6H), 1.9 (AB quartet, J = 10 Hz, 2H, protons at C₈ and C₉), 1.70 (AB quartet, J = 10 Hz, 2H, protons at C₈ and C₉); m/e 82 (C₆H₁₂O²). (Found: C, 52.96; H, 4.88; Br, 34.92; Calc. for C₁₁H₁₅BrO: C, 52.89; H, 4.88, Br, 35.19%).

Rearrangement of 16 with PBr₃

The same procedure as for the rearrangement of 2 with SOCl₂ was used, giving mixture of dibromide 18 and alcohol 19 (contaminated with some of its phosphite ester) which was separated by chromatography over silica. Elution with hexane gave 18 (18%) as a crystalline solid, m.p. 81-82° (EtOH); IR νmax 1095, 855 cm⁻¹; NMR (CDCl₃) δ 2.85-3.25 (m, 6H, 6H), 2.5-2.75 (m, 2H, protons at C₈ and C₉), 2.00 (AB quartet, J = 11 Hz, 4H, protons at C₈ and C₉); m/e 145 (C₈H₁₅Br²). (Found: C, 41.49; H, 3.63; Br, 55.32; Calc. for C₁₁H₁₅Br²: C, 41.41; H, 3.48; Br, 55.11%). Further elution with ether gave alcohol 19 together with a small amount of its phosphite ester.

5,9-Dibromopentacyclo[5,3.0.2.0².0⁶.0³] deca-8-ene 18 from 5,9-dibromopentacyclo[5.3.0.2.0².0⁶.0³] deca-6,10-dione (20)

A soln of di-ketone 20 (1.0 g, 3.1 mmole) in hydrazine hydrate (30 ml, 100%) was refluxed for 4 hr. After cooling, diethylene glycol (70 ml) and KOH (4.5 g) were added. The apparatus was arranged for distillation and the mixture was slowly heated in an oil bath to 220° and which temp was maintained for 3 hr. The mixture was allowed to cool, poured into water and ether extracted. The ether extracts were washed with HCl aq and dried (MgSO₄). Solvent was evaporated giving dibromide 18 (0.4 g, 50%), as a crystalline solid, m.p. 81-82°.
REFERENCES
