Proof of the Stereochemistry of *cis*-2,5-Dibromocyclopentanone†

Mark Boelens, Norbert De Kimpe,* and Marian Keppens

Department of Organic Chemistry, Faculty of Agricultural and Applied Biological Sciences, University of Gent, Coupure Links 653, B-9000 Gent, Belgium

Jean-Paul Declercq

Laboratoire de Chimie Physique et de Cristallographie, Université Catholique de Louvain, 1, Place L. Pasteur, B-1348 Louvain-la-Neuve, Belgium

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The assignment of the long-standing problem of the stereochemistry of *cis*-2,5-dibromocyclopentanone has been performed by stereoselective reduction into *cis*, *cis*-2,5-dibromocyclopentanol, conversion of the latter alcohol into the 4-nitrobenzoate ester, and following ^{1}H NMR and X-ray crystallographic analysis.

Introduction

α,α′-Dibromo ketones have been investigated extensively because of their high synthetic potential. Cyclic and acyclic α,α′-dibromo ketones have served as intermediates for the synthesis of a variety of compounds, including α,β-unsaturated carboxylic acid derivatives,[1] α-alkoxy ketones,[2] α-alkylated ketones,[3] cyclobutanones,[4] 8-oxabicyclo[3.2.1]oct-6-en-3-ones,[5] α-acetoxy ketones,[6] cyclopentanones,[7] tropane alkaloids,[8] cocaine analogues,[9] bicyclo[3.2.1]oct-6-en-3-ones,[10] α-phenylated ketones,[11] α-imino ketones[12] and α-diimines.[12] The generation of oxyallyl cations and the application in natural product synthesis is one of the major accomplishments of the chemistry of α,α′-dibromo ketones.[13–15] Various efforts have been devoted to the study of the stereochemistry of α,α′-dibromocycloalkanones in order to understand differences in reactivity of the stereoisomers.[16] The classical synthesis of 2,5-dibromocyclopentanone **2** from cyclopentanone and bromine in glacial acetic acid[16] or from cyclopentanone and dioxane dibromide[17] gave a single crystalline isomer, the stereochemistry of which was presumptively attributed to trans, based on computer simulation.[16] Previous to the latter study, other papers reported a cis stereochemistry without giving experimental details or the reasoning behind the attribution of the stereochemistry.[18] Several reports did not mention the stereochemistry of 2,5-dibromocyclopentanone[17,19,20] or indicated a trans stereochemistry.[21] A recent paper came to the conclusion that the stereochemistry of the above-mentioned isomer of 2,5-dibromocyclopentanone was cis, based on the synthesis of the dithiocyanato derivative **3**, formed by double nucleophilic substitution.[22] The formation of *trans*-dithiocyanato derivative **4** as a minor isomer (cis/trans ratio 4:1) was explained by S_N2 epimerization of one of the thiocyanato groups by the thiocyanate nucleophile.[22] The stereochemistry of the major isomer **3** was ascertained as cis by means of X-ray crystallographic analysis.[22] However, a base-induced epimerization instead of S_N2 epimerization could also be operative and could be the cause of erroneous results. To this end, efforts were undertaken to clarify the long-standing problems regarding the stereochemistry of 2,5-dibromocyclopentanone.

Results and Discussion

The bromination of cyclopentanone **1** with bromine in glacial acetic acid was performed according to different but similar procedures from the literature,[16,22] each time giving the same crystalline isomer of 2,5-dibromocyclopentanone (mp 66.5–68.5 °C) by crystallization from the reaction mixture. The reaction mixture contained several side products, as visualized by the ^{13}C NMR spectrum, the carbonyl region (δ 195–215) of which displayed seven carbonyl resonances. Among others, signals of elimination products were observed, but the complexity of the ^{13}C NMR spectrum of the reaction mixture precluded any further identification of side products. Recrystallization of this crystalline 2,5-dibromocyclopentanone from chloroform–pentane afforded colorless crystals, suitable for X-ray crystallographic analysis.

Several attempts to obtain an X-ray crystallographic analysis failed due to rapid decomposition of the com-

† Dedicated to Professor H. G. Viehe on the occasion of his 65th birthday.

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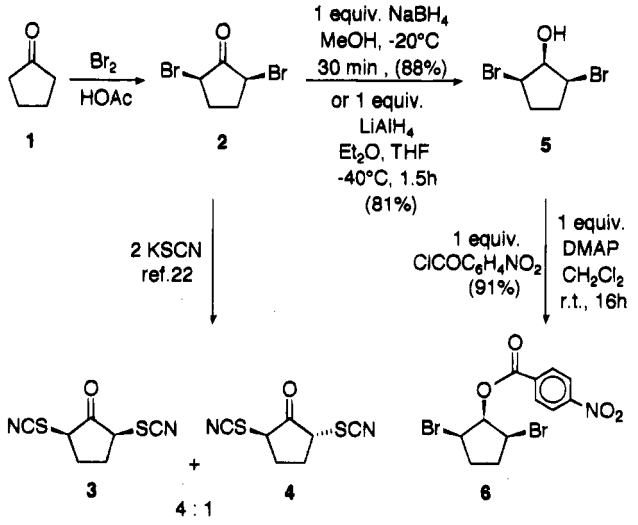
Scheme 1



pound by X-ray irradiation. Nevertheless, low-quality diffraction data were obtained showing that the two halogens were in a cis relationship. However, these data are insufficient to be published. Following this failure, efforts were undertaken to prove the stereochemistry by chemical transformations and detailed NMR analysis of suitable derivatives. It is expected that the reduction of dibromocyclopentanone with cis stereochemistry by hydride under mild reaction conditions results in the stereoselective formation of *cis,cis*-2,5-dibromo-1-cyclopentanol (**5**), as the reduction of *cis*-2,6-dibromocyclohexanone with sodium borohydride in ethanol gave *cis,cis*-2,6-dibromocyclohexanol.[23] The reduction of 2,5-dibromocyclopentanone with trans stereochemistry could be more complex due to subsequent epoxide formation, similar to the six-membered analogue.[23] Reaction of 2,5-dibromocyclopentanone with sodium borohydride in methanol at −20 °C for 30 min gave rise to *cis,cis*-2,5-dibromocyclopentanol (**5**) in 88% yield. A completely similar result was obtained by reduction of 2,5-dibromocyclopentanone with lithium aluminium hydride in ether/THF (1:1) at −40 °C, affording the *cis,cis*-alcohol **5** in 81% yield. The ^{1}H NMR spectrum (270 MHz; $CDCl_3$) of compound **5** revealed a multiplet (1H) at δ 3.98−4.00 for the C*H*O signal and a multiplet (2H) at δ 4.33−4.37 for both C*H*Br signals. The ^{13}C NMR spectrum ($CDCl_3$) showed the expected three resonances at δ 32.49 (*C*H_2-*C*H_2), 51.70 (*C*HBr), and 77.73 (*C*HOH). The conversion of the alcohol **5** into the 4-nitrobenzoate ester **6** was performed with 4-nitrobenzoyl chloride in dichloromethane in the presence of 4-(dimethylamino)pyridine (yield 91%). Recrystallization of compound **6** from diethyl ether in an atmosphere saturated with pentane afforded well-formed single crystals. The ^{1}H NMR spectrum (270 MHz, $CDCl_3$) of compound **6** showed a perfect triplet (J = 4.95 Hz) for the methine hydrogen at position 1, indicative of a cis, cis-stereochemistry. In addition, irradiation of the signal of both C*H*Br units resulted in the appearance of the C*H*O signal as a singlet. The correct structural assignment of compound **6** was unambiguously proven by the X-ray crystallographic analysis, the data of which will be published elsewhere.[26]

In conclusion, evidence is provided regarding the cis-stereochemistry in 2,5-dibromo-1-cyclopentanol derivatives **5** and **6**. The reactions used occur at nonstereogenic atoms, making these results more believable than those based on stereospecific displacements of the bromine atoms.[22] It follows that the long-standing and confusing problem of the stereochemistry of the often used crystalline isomer of 2,5-dibromocyclopentanone is solved and determined to be cis.

Experimental Section

General Methods.[24,25] NMR spectra were recorded on a JEOL JNM EX270 spectrometer. Melting point measurements: Buchi 535 instrument (Kofler hotstage).

***cis*-2,5-Dibromocyclopentanone (2)** was prepared by two methods reported in the literature.[17,22] Crystallization of **2** took place upon prolonged standing at −18 °C (1−3 weeks). Before recrystallization the crude compound was washed with a cold chloroform−pentane mixture (9:1). White needles of *cis*-2,5-dibromocyclopentanone **2** were obtained: mp: 69 °C (lit.[17] mp 68−69 °C, lit.[16] mp 67 °C, lit.[22] mp 64−65.5 °C).

***cis,cis*-2,5-Dibromocyclopentanol (5). Method A.** Sodium borohydride (0.038 g, 1 mmol), dissolved in dry methanol (0.5 mL), was added to a solution of freshly recrystallized *cis*-2,5-dibromocyclopentanone (**2**) (0.242 g, 1 mmol) in absolute methanol (2.5 mL) at −20 °C. After being stirred at this temperature for 0.5 h, the resulting mixture was poured into H_2O and extracted with CH_2Cl_2. The organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel) with ethyl acetate−hexane (40:60) as eluent to give 214 mg of **5** as a colorless oil (88%, R_f = 0.45): IR (NaCl, film) 3472 cm^{-1} (COH); ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.33−2.37 (4H, m), 2.88−2.90 (1H, m), 3.98−4.00 (1H, m), 4.33−4.37 (2H, m); ^{13}C NMR (68 MHz, DEPT, $CDCl_3$) δ 32.49, 51.70, 73.73; MS (70 eV) m/z 242/4/6 (M^+, 11), 163/5(40), 145/7(11), 135/7(12), 106/8(5), 83(42), 57-(100), 55(31). Anal. Calcd for $C_5H_8Br_2O$): C, 24.62; H, 3.31; Br 65.51. Found: C, 24.79; H, 3.44; Br, 65.30.

Method B. To a solution of lithium aluminium hydride (0.015 g, 0.4 mmol) in dry ether (1 mL) was added *cis*-2,5-dibromocyclopentanone (**2**) (0.097 g, 0.4 mmol), dissolved in dry ether (1 mL) and tetrahydrofuran (1 mL), slowly at −40 °C under nitrogen atmosphere. After the mixture was stirred for a period of 1.5 h at −40 °C, a small amount of water (33 μL) was added. The suspension was filtered and dried ($MgSO_4$). After filtration evaporation of the solvent *in vacuo* gave 79 mg (81%) of **5**.

***cis,cis*-2,5-Dibromo-1-cyclopentyl 4-Nitrobenzoate (6).** A mixture of alcohol **5** (200 mg, 0.82 mmol), 4-nitrobenzoyl chloride (154 mg, 0.82 mmol), and 4-(*N,N*-dimethylamino)-pyridine (DMAP, 100 mg, 0.82 mmol) in dichloromethane (5 mL) was stirred at room temperature for a period of 16 h. The reaction mixture was poured into an aqueous hydrogen chloride solution (1 N, 5 mL) and extracted three times with dichloromethane (2 mL). The combined organic phases were washed with water, dried ($MgSO_4$), and concentrated *in vacuo*. Flash column chromatography (silica gel) with ethyl acetate−hexane (10:90) as eluent yielded 293 mg of **6** as a white solid (91%, R_f = 0.28). For the recrystallization the 4-nitrobenzoate ester **6** was dissolved in a small amount of dry Et_2O and placed in a crystallization chamber under a saturated pentane atmosphere at room temperature, affording colorless crystals suitable for the X-ray analysis: Mp 123−124 °C; IR (KBr pellet) 1629 cm^{-1} (C=O); ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.46−2.49 (4H, m), 4.44−4.47 (2H, m), 5.49 (1H, t, J = 4.95 Hz), 8.33 (4H, s); ^{13}C NMR (68 MHz, DEPT, $CDCl_3$) 33.41, 46.15, 75.85, 123.70, 131.14, 134.86, 150.80, 163.43; MS (70 eV) m/z = 391/3/5 (M^+, <1), 312/4 (1), 233 (2), 151 (100), 145/7 (28), 134 (4), 120 (7), 104 (28), 92 (12), 76 (24), 75 (9), 67 (7), 66 (7), 65 (11), 64 (3), 55 (3), 53 (6), 50 (11), 41 (8). Anal. Calcd for $C_{12}H_{11}BrNO_4$: N, 3.56; Br, 40.66. Found: N, 3.69; Br, 40.49.

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