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The bromination of (–)-camphorquinone

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Abstract—The reaction of (–)-camphorquinone with excess moist bromine gives (–)-(1*S*,5*S*)-1-bromomethyl-3,3-dibromo-8,8-dimethyl-7-oxabicyclo[3.2.1]octane-2,6-dione rather than 1-bromomethyl-3,5-dibromo-8,8-dimethyl-7-oxabicyclo[3.2.1]octane-2,6-dione as has been reported in the literature. The controlled reaction of moist bromine with (–)-camphorquinone leads to (–)-(1*S*,5*S*)-3,3-dibromo-1,8,8-trimethyl-7-oxabicyclo[3.2.1]octane-2,6-dione and not to 5-bromo-1-bromomethyl-8,8-dimethyl-7-oxabicyclo[3.2.1]octane-2,6-dione. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

The bromination of camphor has attracted considerable attention, with several of the derived products finding ingenious application as chiral synthons for natural products.[1] (+)-Camphor can be converted into (–)-camphorquinone **1**, and the reaction of this compound with moist bromine was reported by Simonsen et al.[2] to yield a tribromo-derivative $C_{10}H_{11}Br_3O_3$ to which the structure **2** was assigned. We suspected that this structural assignment was incorrect and have now reinvestigated this material and can report that the actual product of the bromination reaction is the closely related compound **3**.

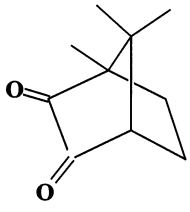
2. Results and discussion

Treatment of (–)-camphorquinone **1** with bromine (4 equiv.) to which a little water has been added led, after a short induction period, to an exothermic reaction which was accompanied by the evolution of substantial quantities of hydrogen bromide. The major product **3** could be isolated from the reaction mixture by trituration with ether, and had mp 201–202°C (lit.[2] 199–200°C) after recrystallisation from ethanol.

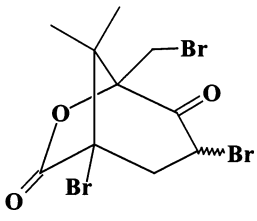
The IR spectrum of **3** includes carbonyl absorptions at 1806 and at 1746 cm^{-1} which can be assigned to its strained γ-lactone and α,α-dibromoketone functions. In the ^1H NMR spectrum of the tribromide **3** there are resonances for the two methyl groups at δ 1.14 and 1.32 ppm and for the bridgehead proton at δ 2.51 (dd, J 3.8 and 3.0 Hz) ppm. The C-5 methylene protons appear as an AB quartet at δ 3.43 and 3.56 ppm that exhibits J_{gem} 15.6 Hz. The 1-bromomethyl group resonates as an AB quartet at δ 3.63 and 3.72 ppm, with J_{gem} 11.4 Hz. These data clearly preclude structure **2** from consideration but do not permit its unambiguous revision to **3**.

The structure of **3** was confirmed by single crystal X-ray analysis, and a projection is shown in Figure 1.

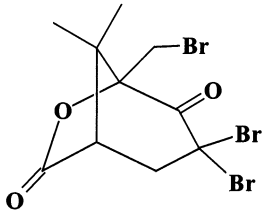
We assign an absolute configuration to **3** on the basis of the mechanistic proposal outlined in Scheme 1. This accommodates the established facts that camphorquinone **1** is converted[3] into the keto-acid **4** when it is treated with strong sulfuric acid, and that this keto acid yields the tribromolactone now known to be **3** when it is treated with excess bromine.[2] Thus, we envisage that triple bromination of the keto acid **4** leads to the α,α,α′-tribromoketone **5** which then loses hydro-



(-)-(1)



(2)



(-)-(3)

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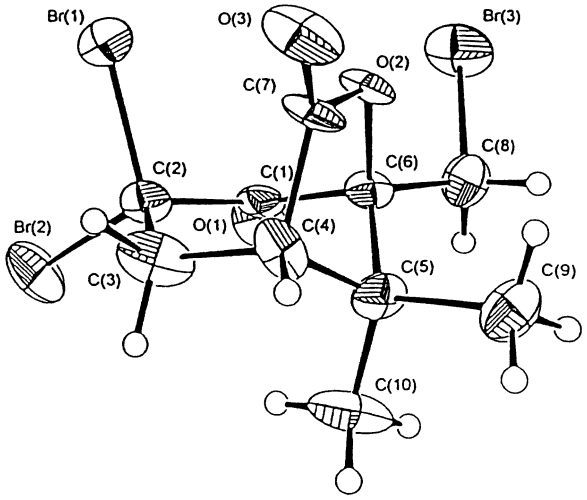
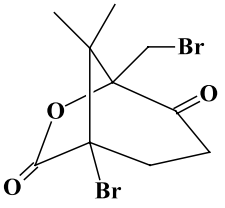


Figure 1.

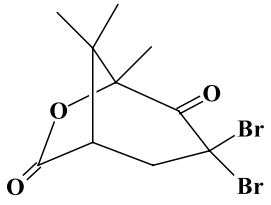
gen bromide to give the unsaturated keto-acid **6**, bromolactonisation of which gives **3**.

Reduction of the tribromolactone **3** using zinc and acetic acid at room temperature gave the monobromolactone **7** which was easily identified from its spectroscopic data. This compound has mp 137–138°C (lit.[2] 144–145°C), and its structure was correctly assigned by Simonsen et al.[2]

Alternatively, when moist bromine was added *slowly* to (−)-camphorquinone **1** under conditions where the reaction temperature was not allowed to exceed 35°C, a dibromolactone having mp 139–140°C could be isolated. This compound has $[\alpha]_D$ −43.3 and $[\alpha]_{546}$ −97.2 in chloroform solutions. Simonsen et al. reported[2] $[\alpha]_{546}$ +40.0 for a similarly prepared compound with mp 137–138°C to which they assigned the structure **8**. However, the dibromolactone which we have obtained using the quoted experimental conditions is clearly the α,α-dibromo compound **9** on the basis of its spectroscopic properties (see Section 3).

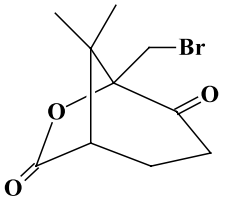


(8)

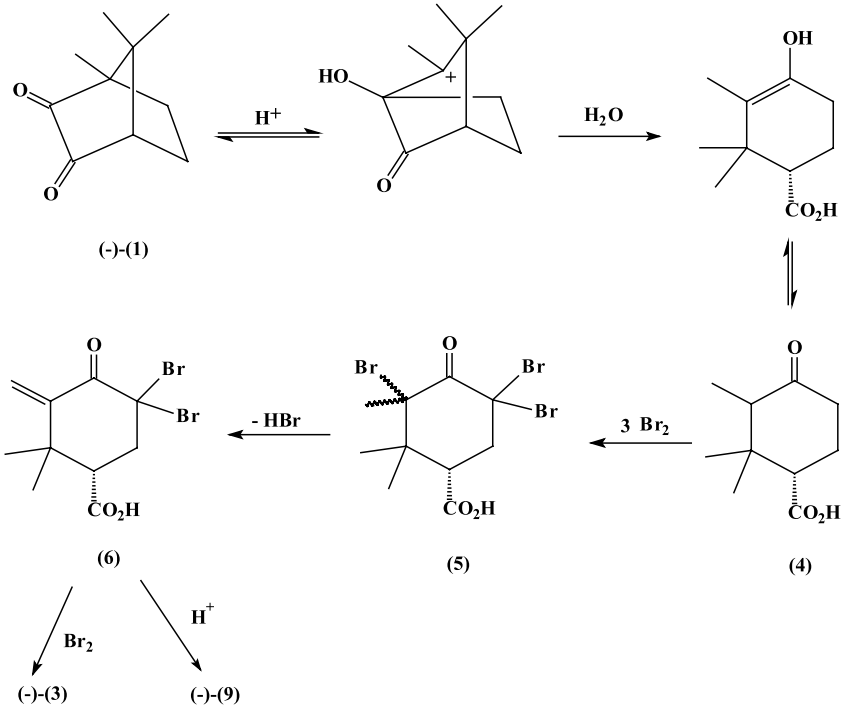


(-)-(9)

The reason for this anomaly remains unclear, but it may be noted that the earlier workers stated[2] that they were unable to reproduce a preparation of what was presumably the same dibromide **9** when employing conditions originally outlined in a paper by Manasse and Samuel.[4] The instability of α,α-dibromoketones on exposure to hydrogen bromide is well documented,[5] and the possibility that a minor variation in reaction conditions may have led to an alternative product in



(+)-(7)



Scheme 1.

our hands cannot be ruled out. The formation of **9** can be rationalised (Scheme 1) by invoking acid-catalysed lactonisation of the unsaturated dibromo-acid **6**.

3. Experimental

3.1. General

NMR spectra were measured for solutions in $CDCl_3$ using JEOL PMX-60 and Bruker MSL-300 spectrometers. IR spectra were obtained for Nujol mulls using a Perkin–Elmer 883 spectrometer. Optical rotations were measured at 20°C using a Perkin–Elmer 141 polarimeter, and $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. All solvents were purified by distillation. (−)-Camphorquinone was prepared by the oxidation of (+)-camphor with selenium dioxide according to a literature procedure.[6] The crystal structure of **3** was obtained using an Enraf-Nonius CAD-4F diffractometer, and was solved by direct methods using SHELXS-86[7] and then refined by full matrix least squares on F^2 using SHELXS-93.[8] Data were corrected for Lorentz and polarisation effects and for absorption.[9] Hydrogen atoms were included in calculated positions with fixed thermal parameters. The non-hydrogen atoms were refined anisotropically. All calculations were performed on a VAX 6610 computer. The ORTEX programme[10] was used to obtain the drawings.

3.2. Crystal data for 3

Colourless orthorhombic crystal; formula $C_{10}H_{11}Br_3O_3$; formula weight 418.92; space group $P2_12_12_1$; unit cell dimensions (Å; °) $a=8.306(1)$ $\alpha=90$, $b=12.569(1)$ $\beta=90$, $c=12.617(1)$ $\gamma=90$; volume 1317.2(2) Å^3; $Z=4$; density (calculated) 2.112 Mg/m^3; absorption coefficient 9.177 mm^{-1}; $F(000)=800$; crystal size 0.35×0.30×0.10 mm; temperature 293 (2) K; wavelength 0.71069 Å; theta range for data collection 2.28–24.89°; index ranges (°) $0\le h\le 9$, $0\le k\le 13$, $0\le l\le 13$; reflections collected 1081; independent reflections 1081; data/restraints/parameters 1081/0/146; goodness-of-fit on F^2 0.414; final R indices [$I>2\sigma(I)$]: $R_1=0.1091$, $wR_2=0.2425$; R indices (all data): $R_1=0.0893$, $wR_2=0.2133$; absolute structure parameter 0.06(6); largest diff. peak and hole 0.718 and −0.637 e A^{-3} (R indices; $R_1=[\Sigma||F_o|-|F_c||]/\Sigma|F_o|$ (based on F), $wR_2=[[\Sigma_w(|F_o-F_c|)^2]/[\Sigma_w(|F_o|)^2]]^{1/2}$ (based on F^2), $w=q/[(\sigma F_o)^2+(a*P)^2+b*P+d+e*\sin(\theta)]$. Goodness-of-fit $=[\Sigma_w(F_o^2|-|F_c^2|)^2/)N_{obs.}-N_{parameters})]^{1/2}$. Tables of crystal data (excluding structure factors) for **3** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 200165. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

3.3. Bromination of (−)-camphorquinone

3.3.1. (−)-(1*S*,5*S*)-1-Bromomethyl-3,3-dibromo-8,8-dimethyl-7-oxabicyclo[3.2.1]octane-2,6-dione, 3. To finely powdered (−)-camphorquinone **1**, ($[\alpha]_D$ −106 (*c* 0.26, $CHCl_3$), 1.0 g), placed in a small, wide-necked conical flask, was added all at once bromine (4.0 g) containing a few drops of water. The reaction mixture became hot after a short interval, and copious amounts of hydrogen bromide were liberated. After this initial reaction had subsided the mixture was heated on a boiling water bath during a further 30 min. Addition of ether to the cooled mixture gave a solid product (2.28 g) that (NMR) consisted largely of a single compound which was recrystallised from ethanol to yield (−)-(1*S*,5*S*)-1-bromomethyl-3,3-dibromo-8,8-dimethyl-7-oxabicyclo[3.2.1]-octane-2,6-dione **3** (1.4 g; 56%), mp 201–202°C, $[\alpha]_D$ −29 (*c* 0.104, $CHCl_3$) (lit.[2] $[\alpha]_D$ −34 {*c* 4.0}), ν_{max} 1806 and 1746 cm^{-1}, δ_H 1.14 (3H, s, Me), 1.32 (3H, s, Me), 2.51 (1H, dd, *J* 3.8 and 3.0, 5-H), 3.43 (1H, part of ABq, *J* 15.6 and 3.8, 4-H$_a$), 3.56 (1H, part of ABq, *J* 15.6 and 3.4, 4-H$_b$), 3.63 and 3.72 (each 1H, Abq, J_{gem} 11.4, -CH_2Br group), δ_C 18.89 and 21.97 (methyl groups), 25.29 (4-CH_2), 46.93 (CH_2Br), 47.20 (quaternary, 8-C), 50.57 (5-CH), 55.42 (quaternary, 3-C), 91.21 (quaternary, 1-C), 172.91 (quaternary, 2-C=O) and 188.59 (quaternary, 6-C=O) ppm. Anal. calcd for $C_{10}H_{11}Br_3O_3$: C, 28.64; H, 2.62; Br, 57.28. Found: C, 28.38; H, 2.69; Br, 57.45%.

3.3.2. (−)-(1*S*,5*S*)-3,3-Dibromo-1,8,8-trimethyl-7-oxabicyclo[3.2.1]octane-2,6-dione, 9. Moist bromine (3 g) was added gradually to stirred, finely powdered (−)-camphorquinone **1** (0.8 g) during 30 min, the reaction mixture being maintained at 35°C. Hydrogen bromide was liberated during this time. The mixture was then warmed on a water bath until gas evolution had ceased. After cooling, the residual gum (1.73 g) was extracted with cold ethanol (20 ml) and the extract was evaporated under reduced pressure. The solid residue (1.28 g), containing (NMR) essentially a single product, was recrystallised with considerable loss from ethanol to give (−)-(1*S*,5*S*)-3,3-dibromo-1,8,8-trimethyl-7-oxabicyclo[3.2.1]octane-2,6-dione **9** (0.41 g; 25%), mp 139–140°C, $[\alpha]_D$ −43.3 (*c* 0.76, $CHCl_3$) and $[\alpha]_{546}$ −97.2 (*c* 0.74, $CHCl_3$), ν_{max} 1790 and 1740 cm^{-1}, δ_H 1.00 (3H, s, Me), 1.20 (3H, s, Me), 1.47 (3H, s, Me), 2.36 (1H, br t, *J* 3.6 Hz, 5-H) and 3.43 (2H, m, 4-CH_2) ppm. Anal. calcd for $C_{10}H_{12}Br_2O_3$: C, 35.29; H, 3.53; Br, 47.05. Found: C, 35.10; H, 3.62; Br, 46.95%.

3.4. Reduction of tribromolactone 3

To a stirred solution of the lactone **3** (0.8 g) in acetic acid (30 ml) was added zinc dust (1.5 g) over 30 min. After stirring for a further 12 h at room temperature, ether (150 ml) was added and the mixture was filtered. The ethereal filtrate was neutralised using sodium hydrogen carbonate solution, washed with water, and dried over anhydrous magnesium sulfate. Evaporation of the solvent yielded a residue which was recrystallised from ether to give (+)-(1*S*,5*S*)-1-bromomethyl-8,8-dimethyl-7-oxabicyclo-[3.2.1]octane-2,6-dione **7** (0.61 g; 80%), mp 137–138°C, $[\alpha]_D$ +68.4 (*c* 0.19) {lit.[2] $[\alpha]_D$ +72.5 (*c* 4.0)}, ν_{max} 1798 and 1735 cm^{-1}, δ_H 1.05 (3H, s, Me), 1.21 (3H, s, Me), 1.95–2.55 (5H, m, 5-H, 3-CH_2 and 4-CH_2) and 3.43 and 3.62 (2H, ABq, J_{gem} 11.1 Hz, CH_2Br) ppm. Anal. calcd for $C_{10}H_{13}BrO_3$: C, 45.97; H, 4.98; Br, 30.65. Found: C, 45.62; H, 4.74; Br, 30.54%.

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