Bicyclo[3.3.1]nonanes as Synthetic Intermediates. XV.[1] Ring Enlargement of Bicyclo[3.3.1]nonane-2,6-dione and Bicyclo[3.3.1]nonan-2-one; Revision of the Literature

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The diazomethane-conducted ring expansion of bicyclo[3.3.1]nonane-2,6-dione (1) was re-examined, and the main product, identified previously as 9-hydroxytricyclo[4.4.0.0^{2,9}]decan-5-one (2), was shown to be 7-hydroxyisotwistan-2-one (6). The ring expansion of bicyclo[3.3.1]nonan-2-one (4) was also re-examined and the ratio of the resulting homologous ketones 10 and 11 was revised to *ca.* 5:1.

Keywords ring expansion; bicyclo[3.3.1]nonane-2,6-dione; bicyclo[3.3.1]nonan-2-one; aldol cyclization; bicyclo[4.3.1]-decanedione; isotwistane; protoadamantane; migratory aptitude; diazomethane

In 1974, Landa and co-workers[3] reported the diazomethane-conducted ring expansion of bicyclo[3.3.1]nonane-2,6-dione **(1)**, claiming that the main product in the reaction was 9-hydroxytricyclo[4.4.0.0^{2,9}]decan-5-one **(2)** on the basis of intensive spectroscopic studies on the product and its half-deoxygenated system assigned as tricyclo[4.4.0.0^{2,9}]decan-9-ol **(3)**. We reinvestigated the reaction and found their assignment for the main product to be incorrect. The ring expansion of bicyclo[3.3.1]nonan-2-one **(4)** was also re-examined, and the erroneous observations and discrepancies reported[3,4] were corrected and/or revised.

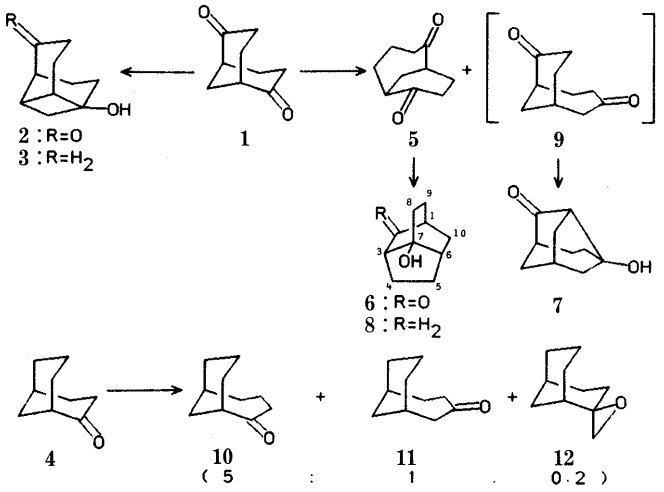

Chart 1

Ring Expansion of 1 According to the method described by Landa *et al.*,[3] the diketone **(1)** was treated with diazomethane formed *in situ* to give a mixture of products. Gas-liquid partition chromatographic (GLPC) analysis showed five main peaks including the one due to *N,N*-dimethyl-*p*-toluenesulfonamide with the highest intensity and the largest retention time. The relative integral ratio for the former four peaks was estimated to be *ca.*1:3:8:2 in the order of increasing retention time. The homologous diketone, bicyclo[4.3.1]decane-2,7-dione **(5)**[5] and methyl *p*-toluenesulfonate were found to be responsible for the second peak on the basis of gas chromatography-mass spectroscopic (GC-MS) studies using a capillary column, and the unchanged starting ketone, hydroxyisotwistanone **(6)**, and 3-hydroxyprotoadamantan-7-one **(7)** for the first, third, and fourth peaks, respectively. Heating the mixture prior to work-up caused complete conversion of the diketone **(5)** into **6** and the relative ratio of the four peaks became 1:1:10:2.

The crude mixture from the "non-heated run" was subjected to column chromatography to give **5**, **6** and **7** with the isolated ratio of *ca.* 0.3:5:1. The physical and spectroscopic properties of both **5** and **6** were identical with those of authentic specimens.[5] The structure of **7** was assigned on the basis of the carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectrum, which showed two singlets, at δ81.8 and δ215.7, due to a quaternary carbon bearing a hydroxyl group and a carbonyl carbon, respectively.

The Huang-Minlon reduction of **6** gave isotwistan-7-ol **(8)**, instead of **3**, as a highly sublimable solid in 55% yield. Its ^{13}C-NMR spectrum showed seven peaks representing four methylenes, two methines and one quaternary carbon, the features substantiating well the symmetric structure of **8**. It is now evident that the reaction proceeded in the normal way, and formation of **6** and **7** in the present experiment is attributed to the base-induced intramolecular aldol cyclization of the ring-expanded products, **5** and bicyclo[4.3.1]decane-3,7-dione **(9)**.

Ring Expansion of 4 Studies on the ring expansion of **4** with diazomethane have been reported independently by two groups.[3,4] The study by Cima and Pietra[4] indicated the product ratio of bicyclo[4.3.1]decan-2-one **(10)** to the -3-one **(11)** to be 3:2. They also reported the formation of a small amount of the *endo*-oxide **(12)** in the reaction. On the other hand, Landa *et al.*[3] found that the 2-ketonic isomer **10** was the only product of the reaction.

The reaction was reinvestigated, and the ketone **4** was treated with diazomethane according to the method described.[4] The GLPC analysis of the crude product showed four main peaks due to the oxide **12**, the starting material **4**, and the ring-expanded ketones **10** and **11**. The ratio of the ketones **10** and **11** was estimated to be *ca.* 5:1 on the basis of both the GLPC and the 500 MHz proton NMR (^{1}H-NMR) analysis of the crude mixture. The integral ratio of two signals, a multiplet centered at δ2.79 and a doublet of doublets at δ2.68, due to the C_1-H of **10** and the C_2-*endo*(α) proton of **11**, respectively, was *ca.* 5:1.

There is continuing interest in application of the reaction

of bridged ketones with diazoalkanes and of bridged β-aminohydrins with nitrous acid to the synthesis of higher homologues of the bridged systems.[6] Application of the reaction to bicyclo[3.3.1]nonanediones thus provides a general method of obtaining tricyclic skeletons from the corresponding bicycles. Reinvestigation of the ring expansion of **4** has now resolved the conflicting results concerning the migratory aptitude in this system.

Experimental

Melting points (mp) are uncorrected. Infrared (IR) spectra were taken with a Hitachi 260-30 or a Shimadzu IR-435 grating spectrometer. ^{1}H- (200 MHz, 500 MHz) and ^{13}C- (50 MHz, 125 MHz) NMR spectra were recorded on a JEOL JNM-FX 200 or a JEOL JNM-GSX500 spectrometer. Coupling constants (*J*) are given in Hz, and the following abbreviations are used; s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad peak. All the NMR spectra were taken for $CDCl_3$ solutions with tetramethylsilane as an internal standard. All the mass spectra (MS) and high-resolution mass spectra (HRMS) were taken on a JEOL JMS-HX 100 mass spectrometer. GLPC was carried out on a Shimadzu GC-9A gas chromatograph, equipped with a glass column (2 mm × 2 m) packed with 10% polyethylene glycol (PEG) on Chromosorb W (60—80 mesh) with N_2 carrier gas (flow rate, 40 ml/min). All the column chromatographies were performed using LiChroprep Si 60 (Merck Art. 9319, particle size 5—20 μm) with a pump (FMI model RP). All the organic extracts were dried over anhydrous magnesium sulfate prior to evaporation.

Treatment of Bicyclo[3.3.1]nonane-2,6-dione (1) with Diazomethane The method of Landa *et al.*[3] was partially modified. *N*-Methyl-*N*-nitroso-*p*-toluenesulfonamide (3.42 g, 16 mmol) was added to a stirred mixture of diketone (**1**, 1.52 g, 10.0 mmol), potassium hydroxide (1.0 g, 18 mmol), methanol (30 ml), and water (2 ml) under ice-cooling. After 1 h of stirring, the amide (1.71 g) and potassium hydroxide (0.5 g) were added, and stirring was continued for another 1 h. The reaction temperature was allowed to rise to ambient temperature, and stirring was continued for additional 1 h. The precipitates formed were filtered off, and the filtrate was concentrated. The residue was diluted with water, and extracted with chloroform. The extract was washed with water and evaporated to give 1.68 g of a pale yellow solid. The GLPC analysis of the solid showed four peaks, with an integral ratio of *ca.* 1 : 3 : 8 : 2, and an additional large peak due to *N,N*-dimethyl-*p*-toluenesulfonamide. The GC-MS analysis with a capillary column (10% PEG on Chromosorb W, 25 m) showed the homologous diketone bicyclo[4.3.1]decane-2,7-dione (**5**) and methyl *p*-toluenesulfonate to be responsible for the second peak, and the reactant (**1**), 7-hydroxyisotwistan-2-one (**6**), and 3-hydroxyprotoadamantan-7-one (**7**) for the first, the third, and the fourth peaks, respectively. Upon heating the reaction mixture at 60°C for 3 h prior to work-up, the relative integral ratio of the four peaks became *ca.* 1 : 1 : 10 : 2. The crude mixture (1.1 g) from the "non-heated run" was subjected to column chromatography [eluent; hexane–acetone (5 : 1, v/v)] to give 33 mg of **5**, 520 mg of **6** and 105 mg of **7**. The physical and spectroscopic properties of **5** and **6** were identical with those of authentic specimens.[5]

5: Colorless needles (from cyclohexane), mp 118—119 °C, lit.,[3] mp 117.3—118.6 °C.

6: Colorless needles (from cyclohexane), mp 213—216 °C,[7] lit., mp 193.7—195.9 °C,[3] mp 121—123 °C,[8] mp 104—108 °C.[9]

7: Colorless solid [sublimed at 150 °C (15 mmHg)], mp 258—260 °C (in a sealed tube). IR(KBr): 3380, 2920, 2845, 1700, 1458, 1448, 1340, 1326, 1228, 1263, 1100, 1070, 1058, 1026, 900 cm^{-1}. ^{1}H-NMR (200 MHz) δ: 1.50—2.18 (9 H, m), 2.30—2.60 (5H, m). ^{13}C-NMR (50 MHz) δ: 26.5 (t), 33.2 (t), 35.5 (d), 40.6 (t), 41.1 (t), 44.3 (d), 45.9 (t), 63.3 (d), 81.8 (s), 215.7 (s). MS *m/z* (%): 166 (M^+, 33), 148 (17), 110 (16), 109 (28), 108 (55), 96 (100), 95 (37), 83 (25), 82 (18), 79 (14), 55 (19). HRMS *m/z*: 166.0992 ($C_{10}H_{14}O_2$ required 166.0993).

Isotwistan-7-ol (8) A mixture of **6** (330 mg, 2.0 mmol), 90% hydrazine hydrate (0.6 ml, 11 mmol), potassium hydroxide (500 mg), and diethylene glycol (10 ml) was stirred at 120—130 °C for 2 h and then at 220—230 °C for 3 h. During the heating at 230 °C, gradual sublimation of the product onto the condenser was observed. The cooled mixture was poured into brine and extracted with ether. The extract was combined with the ether washings of the sublimate, and was washed with brine. Removal of the solvent left 180 mg of a colorless solid, which on sublimation at 150 °C gave 165 mg (55%) of **8** as a colorless solid, mp 129—131 °C (in a sealed tube).[10] IR (KBr): 3290, 2915, 2850, 1450, 1420, 1340, 1300, 1121, 1098, 1066, 939 cm^{-1}. ^{1}H-NMR (200 MHz) δ: 1.10—2.20 (16H, m). ^{13}C-NMR (50 MHz) δ: 23.2 (d), 28.0 (t), 29.6 (t), 32.1 (t), 38.9 (t), 41.4 (d), 79.7 (s). MS *m/z* (%): 152 (M^+, 86), 134 (16), 110 (17), 109 (100), 108 (19), 96 (65), 95 (23), 94 (41), 83 (23), 80 (18), 70 (31), 55 (15). HRMS *m/z*: 152.1178 ($C_{10}H_{16}O$ requires 152.1201).

Treatment of Bicyclo[3.3.1]nonan-2-one (4) with Diazomethane *N*-Methyl-*N*-nitroso-*p*-toluenesulfonamide (513 mg, 2.4 mmol) was added to a mixture of **4** (207 mg, 1.5 mmol), potassium hydroxide (142 mg, 2.5 mmol), methanol (10 ml), and water (1.0 ml) under ice-cooling. After 1 h of stirring, the amide (260 mg) and potassium hydroxide (70 mg) were added, and stirring was continued for another 1 h. Work-up in a manner similar to that for the reaction of **1** gave 310 mg of a pale yellow solid, the GLPC analysis of which showed four main peaks in the ratio of *ca.* 1 : 1 : 10 : 2 in the order of increasing retention time. The first and the second peaks were due to the α-oxide **12** and the starting ketone **4**, and the third and the fourth peaks to the ring-expanded products bicyclo[4.3.1]decan-2-one (**10**) and the -3-one (**11**), respectively. Three hundred milligrams of the solid was subjected to column chromatography [eluent; benzene–hexane (2 : 1, v/v)] to give 107 mg of **10** and 20 mg of **11**.

10: Colorless solid, mp 95—96 °C (in a sealed tube), lit.,[3] mp 82.0—84.2 °C. IR (CCl_4): 2940, 1698, 1460, 1445, 1320, 1185, 1165, 1118, 959, 925 cm^{-1}. ^{1}H-NMR (500 MHz) δ: 1.32—1.52 (3H, m), 1.62—1.90 (7H, m), 2.12—2.18 (2H, m), 2.21 (1H, m), 2.42—2.48 (2H, m), 2.79 (1H, m). ^{13}C-NMR (125 MHz) δ: 21.6 (t), 22.8 (t), 29.6 (t), 30.5 (d), 30.8 (t), 30.9 (t), 36.4 (t), 44.0 (t), 45.8 (d), 218.5 (s). MS *m/z* (%): 152 (M^+, 78), 134 (18), 110 (42), 109 (30), 108 (47), 97 (52), 95 (23), 84 (40), 81 (100), 79 (26), 68 (26), 67 (60). HRMS *m/z*: 152.1201 ($C_{10}H_{16}O$ requires 152.1201).

11: Colorless solid, mp 70—71 °C (in a sealed tube). IR (CCl_4): 2925, 2850, 1708, 1473, 1446, 1330, 1210 cm^{-1}. ^{1}H-NMR (500 MHz) δ: 1.43—1.82 (9H, m), 1.87 (1H, m), 2.13 (2H, m), 2.38—2.48 (3H, m), 2.68 (1H, dd, *J*=12.0, 6.0). ^{13}C-NMR (125 MHz) δ: 16.5 (t), 26.6 (t), 27.5 (d), 29.0 (d), 30.7 (t), 30.9 (t), 32.4 (t), 41.2 (t), 46.3 (t), 214.9 (s). MS *m/z* (%): 152 (M^+, 100), 134 (29), 123 (35), 109 (69), 108 (75), 96 (37), 95 (83), 94 (53), 92 (32), 81 (67), 79 (34), 68 (35), 67 (64), 55 (64). HRMS *m/z*: 152.1182 ($C_{10}H_{16}O$ requires 152.1201).

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References and Notes

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7) The melting point reported[8,9] for **6** is extraordinarily low in comparison with both the present value and that reported by Landa and co-workers[3] (mp 193.7—195.9 °C) as the melting point for the main product of the reaction. The situation was mentioned previously.[5]
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9) M. J. Begley, M. Mellor and G. Pattenden, *J. Chem. Soc., Perkin Trans. 1*, **1983**, 1905.
10) The value reported by Landa and co-workers[3] (mp 132.8—134.7 °C) as the melting point of **3** is in good agreement with the present value.