BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 50 (10), 2811—2812 (1977)

Synthesis and Properties of 2,8-Dioxabicyclo[3.2.1]octane Derivatives

Hajime IRIKAWA, Tsukasa ISHIKURA, and Yasuaki OKUMURA

Department of Chemistry, Faculty of Science, Shizuoka University, Oya, Shizuoka 422

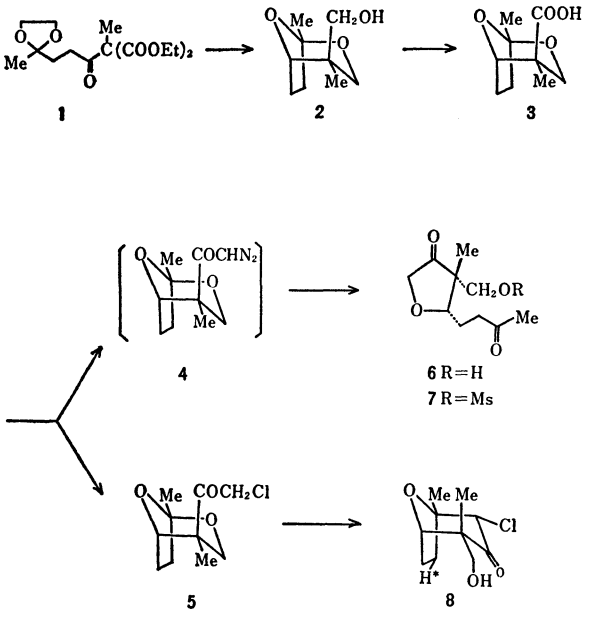
(Received December 13, 1976)

Synopsis. In order to study the isomerization of daphniphylline into isodaphniphylline, 1,4-dimethyl-2,8-dioxabicyclo[3.2.1]octane-4-carboxylic acid (**3**), a degrada tion product of daphniphylline, was synthesized from the keto diester and transformed into the 3-oxacyclopentanones (**6**, **7**).

A *Daphniphyllum* alkaloid, daphniphylline, undergoes isomerization in hydrochloric acid into isodaphniphylline, by which the 2,8-dioxabicyclo[3.2.1]octane structure is transformed into the 3-oxacyclopentanone skeleton.[1] This paper deals with a model reaction of the isomerization, and the synthesis of 1,4-dimethyl-2,8-dioxabicyclo[3.2.1]octane-4-carboxylic acid (**3**), a degradation product of daphniphylline.

Condensation of diethyl methylmalonate with 4,4-ethylenedioxypentanoyl chloride gave the keto diester (**1**), which afforded acetal alcohol (**2**) on reduction with lithium aluminium hydride followed by treatment with hydrochloric acid. Oxidation of **2** with potassium permanganate gave acetal acid (**3**), whose IR and NMR spectra were identical with those of the authentic sample.[1] Thus, *exo* orientation of the hydroxymethyl group in **2** is clear.

For conversion into the 3-oxacyclopentanone skeleton, the sodium salt of **3** was converted into the diazo ketone (**4**) accompanied by the chloro ketone (**5**) with oxalyl dichloride followed by treatment with diazomethane in ether. Treatment of **4** with methanolic hydrochloric acid gave 3-oxacyclopentanone (**6**), which afforded mesylate (**7**). The IR (3670, 3490, 1762, and 1713 cm^{-1}) and NMR (δ 2.19 ppm, 3H, s) spectra of **6** are in line with the assigned structure. The formation of **6**, which bears the substituents shown in the formula, is explained by a nucleophilic attack on the α-keto methylenediazonium group by the 8-oxygen atom in **4** in close proximity.



Scheme

An attempt to convert **5** into **6** by treatment with 30% methanolic hydrogen chloride failed, giving isomeric ketone (**8**) instead. The doublet proton signal at 4.55 ppm (–CHCl–) of **8** is due to the long-range coupling with H*, indicating *endo* configuration of the chlorine atom. The isomerization might proceed through an intermediate, which has an enol group bearing the chlorine atom *trans* to the carbon chain.

By analogy with the conversion of **4** into **6**, the isomerization of daphniphylline seems to involve an intramolecular substitution of the protonated acetoxyl group or protonated hydroxyl group (upon hydrolysis) by the bridge-oxygen in close proximity.

Experimental

All melting points and boiling points are uncorrected. The NMR spectra were obtained on a JNM-C-60H in $CDCl_3$ solution, with TMS as an internal standard.

The Keto Diester **1**. To a mixture of 17.4 g of diethyl methylmalonate, 4.8 g of 50% NaH and 100 ml of ether was added a solution of 4,4-ethylenedioxypentanoyl chloride in 50 ml of ether, prepared from 18.2 g of sodium 4,4-ethylenedioxypentanoate[2] and 18.5 g of oxalyl dichoride. After being stirred at room temperature for 6 h, the reaction mixture was refluxed for 1 h, and worked up in the usual way to give 16.8 g (53.2% from the sodium salt) of **1** as a colorless oil: bp 148—151 °C/1.2 mmHg; IR(neat) 1755 and 1726 cm^{-1}; NMR δ 1.30 (3H, s), 1.30 (6H, t, J=7 Hz), 1.63 (3H, s), 1.96 (2H, m), 2.74 (2H, m), 3.89 (4H, s) and 4.24 ppm (4H, q, J=7 Hz). Found: C, 57.06; H, 7.74%. Calcd for $C_{15}H_{24}O_7$: C, 56.95; H, 7.65%.

The Acetal Alcohol **2**. A mixture of 22.1 g of **1**, 7.6 g of $LiAlH_4$ and 250 ml of ether was refluxed for 6 h, and then treated with 150 ml of 6 M HCl at room temperature overnight. The work-up in the usual way gave 5.1 g (42%) of **2** as a colorless oil: bp 109—110 °C/3.2 mmHg; IR (CCl_4) 3640 and 3480 cm^{-1}; NMR δ 0.74 (3H, s), 1.46 (3H, s), 1.98 (4H, m), 3.22 (1H, s, disappeared on addition of D_2O), 3.40 (1H, d, J=12 Hz), 3.65 (1H, d, J=12 Hz), 3.78 (2H, AB-q, J=11 Hz) and 4.18 ppm (1H, m). Found: C, 63.03; H, 9.43%. Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.36%.

The Acetal Acid **3**. A mixture of 3.1 g of **2**, 0.5 g of NaOH, 6.1 g of $KMnO_4$ and 85 ml of water was stirred at 0 °C for 24 h. Work-up in the usual way gave 1.8 g (55%) of **3** as colorless plates, mp 144—145 °C ($CHCl_3$), whose IR ($CHCl_3$) and NMR spectra were identical with those of the authentic sample. The melting point higher than that of the authentic sample (mp 122—123 °C) indicates that the synthetic **3** is in a form of racemic compound.

Transformation of **3** *into Chloro Ketone* **5** *and Cyclopentanone* **6**. To a mixture of 611 mg of the sodium salt of **3**, 3 drops of

pyridine and 5 ml of benzene was added a solution of 2 ml of oxalyl dichloride in 5 ml of benzene. After being left to stand at room temperature for 3 h, the reaction mixture was concentrated *in vacuo*. Treatment of the residue with ethereal diazomethane (from 5 g of *N*-nitrosomethylurea) at room temperature for 2 days, and then with methanolic hydrochloric acid* (2 ml of 1 M HCl in 3 ml of MeOH) at room temperature for 10 min gave an oily product, which was chromatographed on 5 g of silica gel. Elution with $CHCl_3$ afforded 120 mg (19%) of **5** as colorless needles: mp 76—77 °C (in a sealed tube, diisopropyl ether); IR (Nujol) 1730 cm^{-1}; NMR δ 0.92 (3H, s), 1.47 (3H, s), 2.02 (4H, m), 3.60 (1H, d, J=12 Hz), 4.23 (1H, q, J=12 and 2 Hz), 4.6 (1H, m), and 4.64 ppm (2H, s); MS (70 eV), *m/e*, 218 (M^+), 183 and 141. Found: C, 55.23; H, 7.24%. Calcd for $C_{10}H_{15}O_3Cl$: C, 54.93; H, 6.91%. Elution with 5% MeOH–$CHCl_3$ gave 163 mg (28%) of **6** as a colorless oil; IR ($CHCl_3$) 3670, 3490, 1762, and 1713 cm^{-1}; NMR δ 1.07 (3H, s), 2.00 (2H, m), 2.19 (3H, s), 2.59 (1H, s, disappeared on addition of D_2O), 2.73 (2H, m), 3.69 (2H, s), 3.84 (1H, m), 3.88 (1H, d, J=17 Hz) and 4.12 ppm (1H, d, J=17 Hz); MS (70 eV), *m/e*, 170 (M^+-30), 152, 113, and 112.

The Mesylate **7**. Treatment of 127 mg of **6** with 0.3 ml of methanesulfonyl chloride in 1 ml of pyridine at room temperature for 3 h gave 54 mg (31%) of **7** as colorless plates: mp 90—91 °C (EtOH); IR (Nujol) 1759, 1710, 1348, and 1176 cm^{-1}; NMR δ 1.21 (3H, s), 2.01 (2H, m), 2.21 (3H, s), 2.73 (2H, m), 3.03 (3H, s), 3.88 (1H, q, J=9 and 5 Hz), 3.95 (1H, d, J=17 Hz), 4.15 (1H, d, J=17 Hz), and 4.23 ppm (2H, s); MS (70 eV), *m/e*, 278 (M^+), 221 and 191. Found: C, 47.30; H, 6.55%. Calcd for $C_{11}H_{18}O_6S$: C, 47.47; H, 6.52%.

Isomerization of the Chloro Ketone **5**. A solution of 51 mg of **5** in 5 ml of 30% methanolic hydrogen chloride was refluxed for 3 h. Evaporation *in vacuo* and subsequent crystallization from benzene–hexane gave 31 mg (61%) of **8** as colorless needles: mp 86—88 °C (in a sealed tube); IR (CCl_4) 3610, 3580 and 1720 cm^{-1}; NMR δ 1.42 (3H, s), 1.60 (3H, s), 1.7—2.2 (5H, m), 3.65 (2H, AB-q, J=12 Hz), 4.20 (1H, q, J=5 and 2 Hz) and 4.55 ppm (1H, d, J=2 Hz); MS (70 eV), *m/e*, 218 (M^+), 183 and 165. Found: C, 54.77; H, 7.01%. Calcd for $C_{10}H_{15}O_3Cl$: C, 54.93; H, 6.91%.

* **5** was also obtained on treatment with AcOH instead of methanolic hydrochloric acid.

References

1) H. Irikawa, N. Sakabe, S. Yamamura and Y. Hirata, *Tetrahedron.*, **24**, 5691 (1968).

2) C. K. Warren and B. C. L. Weedon, *J. Chem. Soc.*, **1958**, 3972.