# Norrish Type I Cleavage of 9-Oxabicyclo[3.3.1]nonan-3-one: A Straightforward Synthesis of (±)-(*cis*-6-Methyltetrahydropyran-2-yl)acetic Acid, a Constituent of Civet

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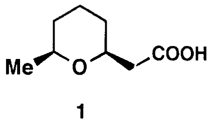
**The photo-reaction of 9-oxabicyclo[3.3.1]nonan-3-one (2) was investigated. Upon irradiation in methanol, the ketone (2) predominantly gave the methanol adduct, 3-hydroxymethyl-9-oxabicyclo[3.3.1]nonan-3-ol (3), accompanied with photo-reduced products, *exo*- and *endo*-9-oxabicyclo[3.3.1]nonan-3-ol (4 and 5). Irradiation in water resulted in Norrish type I cleavage to give directly (*cis*-6-methyltetrahydropyran-2-yl)acetic acid (1), a constituent of civet, in moderate yield.**

**Key words** civet; (*cis*-methyltetrahydropyran-2-yl)acetic acid; photo-reaction; Norrish type I reaction; photo-reduction; 9-oxabicyclo[3.3.1]nonan-3-one

(+)-(*S*,*S*)-(*cis*-6-Methyltetrahydropyran-2-yl)acetic acid ((+)-**1**) was identified as a minor constituent of civet,[1] the expensive glandular secretion of the civet cat, which is utilized in perfumery. The structure was confirmed by synthesis, and more than 20 routes to this compound, including asymmetric syntheses, have been reported.[2] However, many of the attempts to construct stereoselectively the *cis*-2,6-disubstituted tetrahydropyran skeleton suffered from low selectivities and resulted in the concomitant formation of the undesired *trans*-isomer. In addition, generation of the two simple substituents, *i.e.*, methyl and carboxymethyl, required conventional transformations which resulted in lengthy synthetic pathways.

The Norrish type I cleavage of carbonyl compounds is one of the most well-known and widely used procedures in photochemical transformations.[3] Upon irradiation of cyclic ketones in an appropriate solvent, both alkyl and carboxyl functions are simultaneously established in the same molecule.

As part of an investigation into the synthetic applications of the bridged bicyclic system to natural products synthesis,[4] we recently reported the regioselective photocleavage of the 2-substituted 9-azabicyclo[3.3.1]nonan-3-one system,[5] establishing an efficient synthetic route to (−)-indolizidine 223AB, an alkaloid with significant neuromuscular activity isolated from the skin of poison dart frogs. We describe here another application of the photo-reaction to a bicyclic analog, 9-oxabicyclo[3.3.1]nonan-3-one (**2**),[6] which directly gave the acid (**1**) in moderate yield.



**1**

Chart 1

The irradiation of **2** in methanol for 1.7 h gave a mixture of a methanol adduct, 3-hydroxymethyl-9-oxabicyclo[3.3.1]nonan-3-ol (**3**) and photo-reduced products, *exo*- and *endo*-9-oxabicyclo[3.3.1]nonan-3-ol (**4** and **5**).[7] The major product (**3**) displayed a peak at *m*/*z* 172 due to the molecular ion in its MS. Its $^{13}$C-NMR spectrum showed a singlet and a triplet at $\delta$ 71.2 and $\delta$ 70.0 due to carbons bearing a tertiary and a primary hydroxy group, respectively. A doublet at $\delta$ 3.49 ($J=5.6$ Hz) in the $^{1}$H-NMR spectrum changed to a singlet with the addition of $D_2O$, corresponding to the appended hydroxymethyl group.

Both of the photo-reduced products (**4** and **5**) displayed their molecular ion peaks at *m*/*z* 142 in the MS. The $^{1}$H-NMR spectrum of **4** showed a one-proton triplet of triplets at $\delta$ 4.51 ($J=10.5$ and 6.0 Hz) due to the axial carbinol proton in the rigid cyclohexane ring system. The large coupling constant ($J=11.0$ Hz) of the signal at $\delta$ 4.01 due to the carbinol proton of **5** was consistent with a diaxial relationship, implying the tetrahydropyran ring bearing the hydroxyl to be in the boat form.[8] The boat conformation of the ring would also account for the considerable upfield shift of the signals due to $C_7$ and $C_2$($C_4$), which appeared at $\delta$ 12.6 and $\delta$ 35.6, respectively,

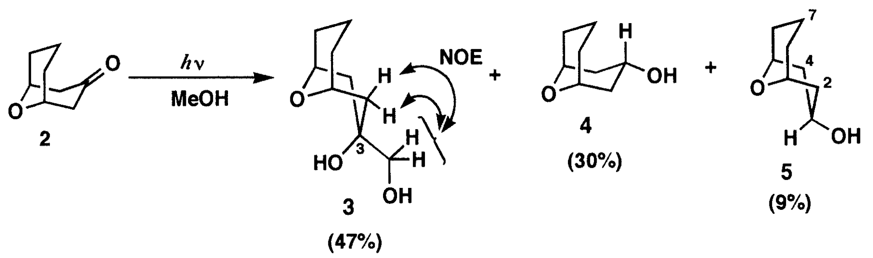


Chart 2

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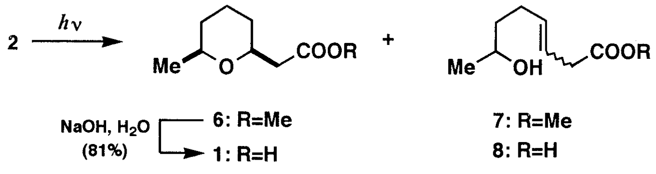

Chart 3

in comparison with those of its counterpart (**4**) at δ 19.0 and δ 40.0.[8)]

The conformation of **3** was found to be chair-boat based on the upfield shift of the signals due to $C_7$ and $C_2(C_4)$, which appeared at δ 12.3 and δ 34.7, respectively, in the $^{13}C$-NMR spectrum. The stereochemistry at $C_3$[9)] was determined on the basis of differential nuclear Overhauser effect (NOE) experiments, where a marked NOE enhancement was observed between the *endo*-proton at $C_2(C_4$, δ 1.48) and the methylene protons (δ 3.49) of the hydroxymethyl group.

All of the products formed upon irradiation in methanol were the result of a hydrogen transfer process between the solvent and the excited state of the ketone to yield a ketyl radical. The ketyl radical could abstract another hydrogen atom from the solvent to give the photo-reduced products (**4** and **5**) or could react with solvent-based radicals to give the mixed pinacol (**3**).[10)]

For the purpose of inhibiting solvent addition, the next irradiation was carried out in acetonitrile, an aprotic solvent with a similar polarity to that of methanol. Upon irradiation of the solution in the presence of 4 eq of methanol as a ketene quencher, the ketone (**2**) afforded the desired type I cleavage product, methyl (*cis*-6-methyltetrahydropyran-2-yl)acetate (**6**), as the main product accompanied with a small amount of a hydroxy-ester, methyl 7-hydroxyoct-3-enoate (**7**).[11)]

The base-catalyzed hydrolysis of **6** gave (±)-**1** in 81% yield; the physical and spectral properties were in accordance with those previously reported.[1a)]

Finally, upon irradiation in water, the ketone (**2**) directly gave the desired acetic acid (±)-**1** in 58% yield with the concomitant formation of a hydroxycarboxylic acid, 7-hydroxyoct-3-enoic acid (**8**).[11,12)] Thus, a straightforward synthesis of (±)-**1** employing the bicyclic system (**2**) has been established.

Photo-irradiation of cyclohexanone in methanol has been reported to give mainly the Norrish type I cleavage product, and photoreduction of the ketone occurs in proton-donor solvents.[3,13)] The effect of the heteroatom in the photo-reaction of 4-heteroatom-substituted cyclo-alkanones has also been reported.[10b,14)] Further studies on the origin of the different reactivities between monocyclic or other 9-heteroatom-substituted bicyclic analogs[15)] and the present one (**2**) are in progress.

## Experimental

Melting points (Yanagimoto MP-S3 micro melting point apparatus) and boiling points are uncorrected. IR spectra were measured on a Shimadzu IR-435 grating infrared spectrophotometer. NMR spectra were recorded on a JEOL JNM-GSX 270 (270 MHz $^1H$, 67.5 MHz $^{13}C$) or a JEOL JNM-GSX 500 (500 MHz $^1H$, 125 MHz $^{13}C$) spectrometer. Chemical shifts and coupling constants (*J*) are given in δ values (ppm) and in hertz (Hz), respectively, and the following abbreviations are used; s = singlet, d = doublet, t = triplet, m = multiplet, br = broad peak. All the NMR spectra were taken for $CDCl_3$ solutions with tetramethylsilane as an internal standard. Low-resolution mass spectra (MS) and high-resolution mass spectra (HRMS) were recorded on a Shimadzu QP 1000EX or a JEOL JMS-HX 100 spectrometer. Photochemical reactions were carried out in an immersion apparatus fitted with an Ishii UV-HT 200 W high-pressure mercury lamp under argon using degassed solvent. Column chromatography was effected over Merck Kieselgel 60 (230—400 mesh) with a pump (FMI model RP). All the organic extracts were dried over anhydrous magnesium sulfate prior to evaporation.

**9-Oxabicyclo[3.3.1]nonan-3-one (2)** A mixture of methyl 3-hydroxy-9-oxabicyclo[3.3.1]non-2-ene-2-carboxylate[16)] (900 mg, 4.5 mmol), potassium hydroxide (763 mg, 13.6 mmol), dimethylsulfoxide (20 ml), and water (8 ml) was heated at 140 °C for 3 h. After being cooled, the reaction mixture was poured into brine (20 ml) and extracted with cyclohexane. The extract was washed with brine, and evaporated to give a colorless solid (628 mg), which, on recrystallization from *n*-hexane, gave **2** (605 mg, 95%) as colorless needles, mp 80.5—81.5 °C (lit.,[6)] mp 76—80 °C). The spectral data were in agreement with those reported.[6)]

**Photolysis of 2 in Methanol** A mixture of **2** (96 mg, 0.69 mmol) and methanol (200 ml) was irradiated for 1.7 h. Removal of the solvent left a pale yellow oil (112 mg), which, on column chromatography (*n*-hexane–acetone, 4 : 1, v/v), gave 3-(hydroxymethyl)-9-oxabicyclo[3.3.1]-nonan-3-ol (**3**) (55 mg, 47%), 9-oxabicyclo[3.3.1]nonan-3β-ol (**4**) (29 mg, 30%), and 9-oxabicyclo[3.3.1]nonan-3α-ol (**5**) (9 mg, 9%).

**3**: Colorless oil, bp 108—110 °C (5 mmHg). IR ($CHCl_3$): 3510 $cm^{-1}$. $^1H$-NMR δ: 1.35—1.40 (2H, m), 1.48 (2H, dd, *J* = 13.5, 4.5), 1.52—1.59 (1H, m), 1.82—1.93 (3H, m), 2.10 (1H, t, *J* = 5.6, exchangeable with $D_2O$), 2.14—2.21 (2H, m), 3.49 (2H, d, *J* = 5.6), 3.76 (1H, s, exchangeable with $D_2O$), 4.29—4.34 (2H, m). $^{13}C$-NMR δ: 12.3 (t), 30.5 (t), 34.7 (t), 66.2 (d), 70.0 (t), 71.2 (s). MS *m/z* (%): 172 ($M^+$, 0.1), 141 (100), 95 (30), 81 (47), 55 (57). HRMS *m/z*: 172.1122 ($C_9H_{16}O_3$ requires 172.1100).

**4**: Colorless oil, bp 70—72 °C (4 mmHg). IR ($CHCl_3$): 3589, 3422 $cm^{-1}$. $^1H$-NMR δ: 1.53 (2H, dm, *J* = 14.0), 1.58—1.75 (3H, m, including hydroxyl proton), 1.80—1.87 (2H, m), 1.94—2.03 (4H, m), 4.15 (2H, br t-like, *J* = 6.0), 4.51 (1H, tt, *J* = 10.5, 6.0). $^{13}C$-NMR δ: 19.0 (t), 29.1 (t), 40.0 (t), 64.0 (d), 68.2 (d). MS *m/z* (%): 142 ($M^+$, 17), 124 (6), 101 (79), 81 (64), 73 (100), 55 (77). HRMS *m/z*: 142.0987 ($C_8H_{14}O_2$ requires 142.0994).

**5**: Colorless oil, bp 69—71 °C (4 mmHg). IR ($CHCl_3$): 3586, 3409 $cm^{-1}$. $^1H$-NMR δ: 1.32—1.40 (4H, m), 1.54 (1H, dm, *J* = 14.0), 1.81 (2H, tt, *J* = 14.0, 4.2), 2.08 (1H, dtt, *J* = 14.0, 14.0, 4.2), 2.21 (1H, brs, exchangeable with $D_2O$), 2.29—2.37 (2H, m), 4.01 (1H, tt, *J* = 11.0, 6.0), 4.20 (2H, ddd, *J* = 9.1, 5.0, 4.2). $^{13}C$-NMR δ: 12.6 (t), 30.5 (t), 35.6 (t) 62.9 (d), 66.8 (d). MS *m/z* (%): 142 ($M^+$, 10), 124 (13), 101 (78), 81 (80), 73 (93), 55 (100). HRMS *m/z*: 142.0986 ($C_8H_{14}O_2$ requires 142.0994).

**Photolysis of 2 in Acetonitrile in the Presence of Methanol** A mixture of **2** (100 mg, 0.71 mmol), acetonitrile (200 ml), and methanol (115 μl, 2.84 mmol) was irradiated for 2.5 h. Removal of the solvent left a pale yellow oil (121 mg), which, on column chromatography (*n*-hexane–ethyl acetate, 25 : 1, v/v), gave methyl (*cis*-6-methyltetrahydropyran-2-yl)acetate (**6**) (74 mg, 60%), a 1.6 : 1 mixture of methyl *E*- and *Z*-7-hydroxyoct-3-enoate (**7**) (18 mg, 15%), and the starting material (8.4 mg, 8%).

**6**: Colorless oil, bp 83—85 °C (8 mmHg), lit.,[1a)] bp 92 °C (10 mmHg). The spectral data were in agreement with those reported.[1a)]

Mixture of *E*- and *Z*-Octenoate (**7**): Colorless oil, bp 145—148 °C (3 mmHg). IR ($CHCl_3$): 3590, 3450, 1730 $cm^{-1}$. $^1H$-NMR δ: 1.19 (1.85H, d, *J* = 6.2), 1.20 (1.15H, d, *J* = 6.2), 1.50—1.57 (2H, m), 1.64 (1H, brs, exchangeable with $D_2O$), 2.10—2.22 (2H, m), 3.04 (1H, d-like, *J* = 6.2), 3.06—3.18 (1H, m), 3.68 (1.85H, s), 3.69 (1.15H, s), 3.77—3.85 (1H, m), 5.52—5.64 (2H, m). $^{13}C$-NMR δ: 23.5 (q), 23.6 (q), 23.7 (t), 28.9 (t), 32.8 (t), 37.8 (t), 38.4 (t), 51.8 (q), 51.9 (q), 67.2 (d), 67.6 (d), 121.2 (d), 122.0 (d), 133.2 (d), 134.3 (d), 172.6 (s). MS *m/z* (%): 172 ($M^+$, 1), 154 (22), 128 (62), 113 (40), 94 (100), 81 (73), 74 (72), 67 (58). HRMS *m/z*: 172.1125 ($C_9H_{16}O_3$ requires 172.1099).

**(*cis*-6-Methyltetrahydropyran-2-yl)acetic Acid (1)** A mixture of **6** (50 mg, 0.29 mmol), sodium hydroxide (35 mg), methanol (2 ml), and water (4 ml) was heated at 60 °C for 5 h. After being cooled, the reaction mixture was poured into brine (10 ml), and washed with diethyl ether. The aqueous layer was acidified with 5% hydrochloric acid, and extracted with diethyl ether. The extract was washed with brine, and evaporated to give a colorless solid (41 mg), which, on recrystallization from pentane, gave **1** (37 mg, 81%) as colorless needles, mp 50—51 °C, lit.,[1a)] mp 52—53 °C. The spectral data were in agreement with those reported.[1a)]

**Photolysis of 2 in Water** A mixture of **2** (100 mg, 0.71 mmol) and water (200 ml) was irradiated for 25 min. Removal of the solvent left a colorless oil (106 mg), which, on column chromatography ($CHCl_3$–EtOH, 30:1, v/v), gave **1** (65 mg, 58%), a 1.6:1 mixture of *E*- and *Z*-7-hydroxyoct-3-enoic acid (**8**) (17.8 mg, 16%), and the starting material (13 mg, 13%). The physical and spectral properties of **1** were completely in accord with those of the specimen obtained by the hydrolysis of **6**.

Mixture of *E*- and *Z*-Octenoic Acid (**8**): Colorless oil, bp 153—156 °C (0.03 mmHg). IR ($CHCl_3$): 3500—2500, 1711 $cm^{-1}$. $^1H$-NMR $\delta$: 1.19 (1.85H, d, $J=6.0$), 1.20 (1.15H, d, $J=6.0$), 1.47—1.60 (2H, m), 2.10—2.22 (2H, m), 3.06 (1H, d-like, $J=6.0$), 3.09—3.22 (1H, m), 3.78—3.88 (1H, m), 5.30 (2H, br s, exchangeable with $D_2O$), 5.52—5.65 (2H, m). $^{13}C$-NMR $\delta$: 23.3 (q), 23.4 (q), 23.7 (t), 28.8 (t), 32.7 (t), 37.7 (t), 38.2 (t), 67.4 (d), 67.8 (d), 120.9 (d), 121.6 (d), 133.4 (d), 134.7 (d), 177.2 (s). MS *m/z* (%): 158 ($M^+$, 0.6), 140 (54), 114 (35), 95 (62), 81 (100), 67 (55), 55 (70). HRMS *m/z*: 158.0935 ($C_8H_{14}O_3$ requires 158.0943).

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