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Bicyclo[3.3.1]nonanes as Synthetic Intermediates. IX.[1] Photo-Irradiation of Bicyclo[3.*n*.1]alkan-3-one in Cyclohexane: A Selective Photo-Reduction with Predominance of *endo*-Hydrogenation

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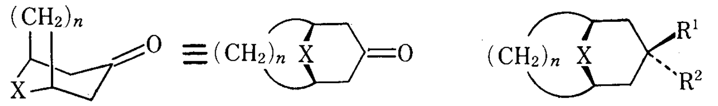
Predominant formation of *exo*-alcohols in the photo-irradiation of bicyclo[3.3.1]nonan-3-one and its analogs is described.

Keywords——bicyclo[3.3.1]nonane system; selective photo-reduction; steric hindrance; intermolecular hydrogen abstraction; hydrogen-donor solvent.

Owing to its unique conformational features, intensive studies on the bicyclo[3.3.1]nonane system bearing substituents at the "fork head" have been made; the specific chemical behavior of this system is exemplified by the anomalous inactivity of bicyclo[3.3.1]nonan-3-one (**1**)[3] and related systems against nucleophiles.[4] The conversion of **1** into the corresponding *exo*-alcohol, bicyclo[3.3.1]nonan-3β-ol (**2**),[3a,d] for example, seems to be trivial, but the conventional methods involving metal hydride reduction[3a,5] or hydrogenation[6] were reported to be retarded to some extent and to give exclusively the *endo*-alcohol, bicyclo[3.3.1]nonan-3α-ol (**3**).[3a,5] Only the dissolving metal reduction[5a] was reported to give the *exo*-isomer (**2**) in 47% yield.

This paper deals with the photo-irradiation of **1** and its 9-aza analog, methyl 3-oxo-9-azabicyclo[3.3.1]nonane-9-carboxylate (**4**),[7] and of bicyclo[3.2.1]octan-3-one (**5**)[3c,d,8] in cyclohexane, where the reduction to *exo*-alcohols was found to occur to a considerable extent.



1: $n=3$, $X=CH_2$
4: $n=3$, $X=NCOOMe$
5: $n=2$, $X=CH_2$

2: $n=3$, $X=CH_2$, $R^1=OH$, $R^2=H$
3: $n=3$, $X=CH_2$, $R^1=H$, $R^2=OH$
7: $n=3$, $X=NCOOMe$, $R^1=OH$, $R^2=H$
8: $n=3$, $X=NCOOMe$, $R^1=H$, $R^2=OH$
9: $n=2$, $X=CH_2$, $R^1=OH$, $R^2=H$
10: $n=2$, $X=CH_2$, $R^1=H$, $R^2=OH$

Chart

Direct irradiation of **1** in cyclohexane afforded a 4:1 mixture of *exo* and *endo* stereoisomers, **2** and **3**, in 54% isolated yield together with bicyclohexyl (**6**).[9] The irradiation in ethanol under similar conditions also gave a mixture with predominance of the former (**2**) in 41% yield.

As the carbonyl group of the system is highly hindered by the trimethylene bridge at the

β,β' positions, it is difficult for the solvent to obtain access from the *endo* side in the "twin chair" conformation to the pyramidal radical center formed as an intermediate. A possible explanation for the predominant formation of the *exo*-alcohol may be given in terms of "intramolecular" hydrogen abstraction of the C_7-*endo* hydrogen by the ketyl radical.

In an attempt to clarify the origin of the C_3–H in **2**, we examined the irradiation of **1** in cyclohexane-d_{12}, but consumption of the ketone was markedly retarded and no detectable amount of the alcohol (**2**) derived from the "intramolecular" process, or of the deuterio alcohols from the "intermolecular" process, was formed. The failure of the "type II" intramolecular abstraction of the C_7-*endo* hydrogen close to the carbonyl at C_3[10)] can be attributed to lack of the stereoelectronic requirement, as proposed by Turro and Weiss.[11)] The deuterium isotope effect observed in the present experiment suggests that the rate-determining step is at the stage of the "intermolecular" hydrogen abstraction from cyclohexane.[12)]

Irradiation of the 9-aza analog (**4**) in cyclohexane under similar conditions also resulted in the formation of a mixture of the corresponding alcohols, methyl 3β- and 3α-hydroxy-9-azabicyclo[3.3.1]nonane-9-carboxylate (**7** and **8**), with predominance of the former, in 55% yield. Exclusive formation of the *endo*-alcohol (**8**) was achieved by the sodium borohydride (SBH) reduction of **4** in 89% isolated yield.

Irradiation of **5** in cyclohexane also proceeded in a similar way to give the corresponding photo-reduced products, *exo*- and *endo*-bicyclo[3.2.1]octan-3-ol (**9** and **10**)[3d,8c)] as a 13:1 mixture[13)] in 52% yield.

Lattes and co-workers[14)] reported that cyclohexanones lacking α-substituents were photo-reduced to diastereomeric cyclohexanols on irradiation in hydrogen-donor solvents, while the "type-I" (α-) and "type-II" cleavages are two of the best-known photochemical processes for alkanones.

The present results clearly demonstrate that the absence of α-substituents on the cyclohexanone ring in the bicyclic system, as in the monocyclic case, is essential for retarding the photolysis[15)] and resulting in the photo-reduction. However, these results do not include a transannular reaction, and are consistent with the hypothesis proposed by Turro and Weiss.[11)] This is a novel example of the predominant formation of *exo*-alcohols from the corresponding bicyclic "fork head" ketones, and is an interesting manifestation of the specificity encountered in these systems.

Experimental

An Eikosha PIH-300 350W high-pressure mercury lamp was used for photo-irradiation. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were taken for 10% solutions in CCl_4 or $CDCl_3$ with a Hitachi R-22 spectrometer, with tetramethylsilane as an internal standard. Gas liquid partition chromatography (GLPC) was done on a Perkin-Elmer 800 gas chromatograph with a stainless steel column (2 mm × 1.8 m) packed with 1.5% SE-52 on Chromosorb W (60—80 mesh) with N_2 carrier gas at a flow rate of 30 ml/min. Gas chromatography-mass spectra (GC-MS)[16)] were taken on a JEOL JMS-D100/JGC-20K system, in conjunction with a JEC-6 spectrum computer, equipped with a glass column (3 mm × 1 m) packed with 1.5% OV-17 on Chromosorb W (80—100 mesh) with helium carrier gas at a flow rate of 40 ml/min. High-resolution MS were taken with a JEOL JMS-D300 mass spectrometer. Column chromatography was performed on Merck Aluminiumoxid 90 (Aktivitätsstufe II-III), unless otherwise mentioned.

Irradiation of Bicyclo[3.3.1]nonan-3-one (1)——General Procedure: A solution of **1** (200 mg, 1.4 mmol) in cyclohexane (20 ml) was irradiated for 5 h at 5 °C under nitrogen with the high-pressure mercury lamp. After removal of the solvent under reduced pressure, the residue was subjected to column chromatography. The first fraction (eluent: pentane) gave 100 mg of bicyclohexyl (**6**), bp 120 °C (25 mmHg) [lit.[9)] bp 238 °C (760 mmHg)], and the second fraction (eluent: chloroform) gave an unidentified mixture (108 mg). The third fraction (eluent: chloroform) gave a highly sublimable solid, which was a mixture of isomeric alcohols (110 mg, 54%), **2** and **3**, in a ratio of 4:1. The ratio was determined by integration of the carbinol proton resonances in ^{1}H-NMR at δ 4.26 and δ 3.48 ppm for **2** and **3**, respectively, and was confirmed for the corresponding acetates by GLPC measurement after treatment of the crude mixture with Ac_2O/Py. The structural assignment of the isomeric alcohols **2** and **3** was performed by comparison of the GC-MS spectra with those of authentic specimens prepared according to the known methods.[3d,5a)]

Irradiation of 1 in Ethanol——A solution of **1** (103 mg, 0.75 mmol) in ethanol (10 ml) was treated for 7 h according to the general procedure to give a 3 : 1 mixture (43 mg, 41%) of **2** and **3**, together with an unidentified mixture (32 mg).

Irradiation of 1 in Cyclohexane-d_{12}——A solution of **1** (103 mg, 0.75 mmol) in cyclohexane-d_{12} (10 ml) was irradiated for 5 h under the same conditions as those in the general procedure. No consumption of the ketone (**1**) nor photo-reduction was detected on GC-MS inspection of the mixture. Even after irradiation for 48 h, no detectable amount of the corresponding deuterio alcohols, or of deuterio bicyclohexyl, was observed by GC-MS, infrared (IR) and ^{1}H-NMR measurement of the crude mixture.

SBH Reduction of 4——A mixture of **4** (100 mg, 0.5 mmol) and SBH (150 mg, 4.0 mmol) in methanol (15 ml) was stirred for 18 h at room temperature. The mixture was diluted with water and extracted with chloroform. The extract was worked up in a usual manner to give 103 mg of a colorless oil, which on distillation under reduced pressure gave 90 mg (89%) of **8** as a colorless oil, bp 99 °C (0.003 mmHg). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3470, 2940, 1695, 1450, 1332, 1100. ^{1}H-NMR (CCl_4) δ: 1.00—2.50 (10H, m, ring methylene), 3.50 (1H, m, C_3–H), 3.62 (3H, s, $COOCH_3$), 4.32 (2H, m, $C_{1,5}$–H). MS *m/e* (%): 199 (M^+, 23), 140 (100). High-resolution MS *m/e*: Found 199.122. Calcd for $C_{10}H_{17}NO_3$ (M^+): 199.121. Acetate: bp 115 °C (0.02 mmHg). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 2935, 1744, 1701, 1450, 1240, 1100. ^{1}H-NMR (CCl_4) δ: 1.20—2.50 (10H, m, ring methylene), 1.96 (3H, s, $OCOCH_3$), 3.60 (3H, s, $COOCH_3$), 4.37 (2H, m, $C_{1,5}$–H), 4.70 (1H, m, C_3–H). MS *m/e* (%): 241 (M^+, 15), 138 (100). High-resolution MS *m/e*: Found 241.133. Calcd for $C_{12}H_{19}NO_4$ (M^+): 241.132.

Irradiation of 4——A solution of **4** (197 mg, 1.0 mmol) in cyclohexane (20 ml) was treated for 20 h according to the general procedure. During the irradiation, formation of unidentified white precipitates was observed. After removal of the precipitates and of the solvent, the residue was washed with *n*-pentane. The pentane-insoluble portion gave 96 mg of a colorless oil (a mixture of **7** and **8**). From the pentane solution, 88 mg of bicyclohexyl (**6**) and 14 mg of the mixture of **7** and **8** were obtained. The total yield of the alcohols was 55%.

The product ratio was determined to be 3 : 2 by integration of the resonances of the C_3-protons in the ^{1}H-NMR at δ 5.49 and δ 4.70 for the *exo*- and the *endo*-isomer, respectively, after conversion of the mixture to the corresponding acetates in 92% yield. Column chromatography of the mixture (95 mg) with chloroform as the eluent gave 24 mg of the acetate of the *endo*-isomer as the first fraction; the spectral data were completely in accordance with those of an authentic specimen obtained by the SBH reduction of **4**. The second fraction provided 44 mg of the *exo*-acetate as a colorless oil, bp 128 °C (0.008 mmHg). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 2950, 1742, 1703, 1450, 1242, 1105, 1030. ^{1}H-NMR (CCl_4) δ: 1.40—2.15 (10H, m, ring methylene), 1.93 (3H, s, $OCOCH_3$), 3.62 (3H, s, $COOCH_3$), 4.34 (2H, m, $C_{1,5}$–H), 5.49 (1H, nine-line pattern, C_3–H). MS *m/e* (%): 241 (M^+, 14), 138 (100). High-resolution MS *m/e*: Found 241.130. Calcd for $C_{12}H_{19}NO_4$ (M^+): 241.132.

Irradiation of Bicyclo[3.2.1]octan-3-one (5)——A solution of **5** (186 mg, 1.5 mmol) in cyclohexane (20 ml) was treated for 20 h according to the general procedure to give a 13 : 1 mixture of **9** and **10** in 52% yield (98 mg) along with **6** (91 mg). The product ratio was determined by GLPC measurement, and the structural assignment of the products was performed by comparison of the GC-MS spectra with those of authentic specimens prepared according to published methods.[3d,8c)]

Irradiation of 4-*tert*-Butylcyclohexanone——A solution of 4-*tert*-butylcyclohexanone (1.0 g, 6.5 mmol) in cyclohexane (80 ml) was irradiated for 45 h according to the general procedure to give 0.45 g (44%) of a mixture of *trans*- and *cis*-*tert*-butylcyclohexanol as a colorless solid in a ratio of 4 : 1, as determined by ^{1}H-NMR integration of carbinol proton resonances at δ 3.49 and at δ 4.02 ppm for the *trans*- and the *cis*-isomer, respectively.

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