Strain in a Bicyclo[3.3.0]oct-1-ene. Preparation of 5,8-Dimethylbicyclo[3.3.0]oct-8-en-2-one and Related Compounds

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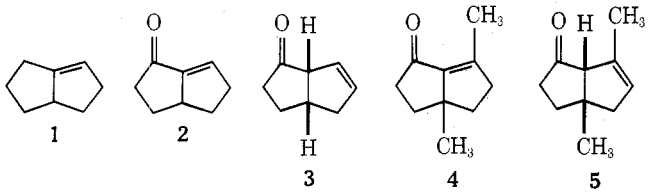
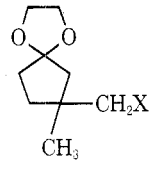
Pyrolysis of the acetylenic cyclopentanone **11** furnishes **4** and **13** in 94% yield. **4** is formed from secondary rearrangement of **13**; this reaction is reversible; and the equilibrium ratio at ~380° is 69:31 (**4**:**13**). Base-catalyzed enolization of **4** leads to equilibration with unconjugated isomer **5**; here the equilibrium ratio is 3:97 (**4**:**5**), corresponding to a free energy difference of ~2.4 kcal/mol in favor of **5**.

The presence of a double bond at the bridgehead in bicyclo[3.3.0]oct-1-ene (**1**) should introduce significant angle strain in the carbon skeleton. Very few compounds incorporating this feature have been described, however, and there is no information available concerning the relative stability of this strained system. The simple conjugated ketone **2**, for example, remains unknown, although its β,γ-unsaturated isomer **3** has been synthesized by at least three routes and has been exposed to conditions which presumably could have led to shift of the double bond into conjugation.[1] This suggests that ketones such as **2** cannot be approached synthetically by way of their β,γ isomers, and furthermore that they may well not survive exposure to acid or base, since these enolizing conditions could lead to deconjugation of the double bond. In the present report we describe preparation of an alkylated derivative of **2**, 5,8-dimethylbicyclo[3.3.0]oct-8-en-2-one (**4**),[2] along with observations on its base-catalyzed equilibration with the less strained β,γ isomer **5**.

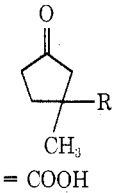


1 **2** **3** **4** **5**

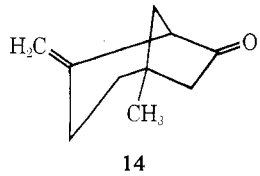
The synthetic sequence began with **6**, prepared as previously described by ketalization and hydride reduction of keto acid **7**.[3] Hydroxy ketal **6** was converted via tosylate **8**



6, X = OH
8, X = OTs
9, X = I
10, X = $CH_2C{\equiv}CSi(CH_3)_3$

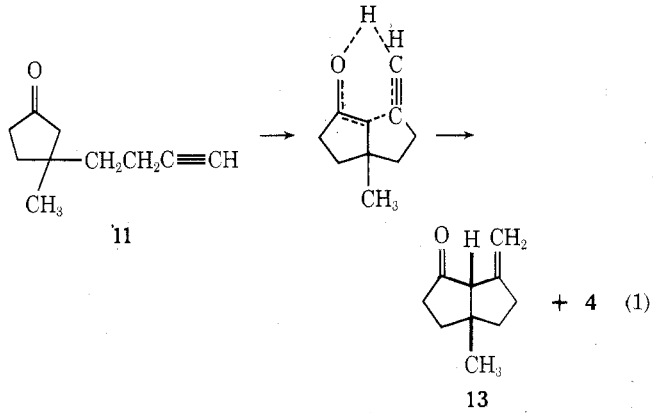


7, R = COOH
12, R = $CH_2CH_2CH_2CH_3$



14

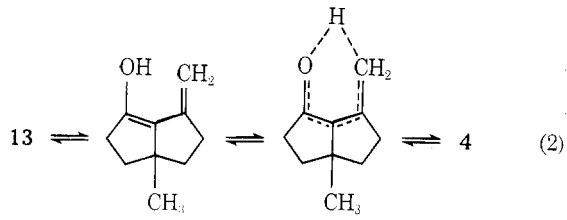
into the iodide **9**. This displacement of a neopentyl tosylate took place very efficiently (91% yield after distillation) using sodium iodide in warm hexamethylphosphoramide.[4] A second substitution at this hindered center occurred upon treatment of **9** in the same solvent with lithio-1-trimethylsilylpropyne[5] to form **10**. Earlier workers have commented on the particular effectiveness of hexamethylphosphoramide as solvent in neopentyl substitution reactions,[6] and our results here are in line with this experience. Exposure of **10** to aqueous ethanolic silver nitrate followed by potassium cyanide led to removal of both protecting groups and formation of ketone **11**. This treatment with silver(I) is a known[7] method for desilylation of protected acetylenes, and the changes involved in converting **10** into the intermediate silver acetylide render the aqueous alcoholic medium sufficiently acidic (apparent pH ~2) to permit concomitant acid hydrolysis of the ethylene ketal. The structure of **11** was confirmed by catalytic hydrogenation of the triple bond to furnish the corresponding butyl compound **12**. A comparison sample of **12** was available through conjugate addition of lithium dibutylcuprate[8] to 3-methyl-2-cyclopentenone. The acetylenic ketone **11** was then pyrolyzed in an evacuated sealed tube for 7 min at ~380° to furnish a mixture of bicyclic ketones **4** and **13** in 94% yield (eq 1).



11 **13** + **4** (1)

While thermal cyclization of various unsaturated ketones has been the subject of detailed study,[9] there are on record very few examples of this transformation leading to bicyclo[3.3.0]octanes,[10] or involving alkynes[11] rather than alkenes. Ketones **4** and **13** were separated by preparative vapor phase chromatography (VPC) and their structures assigned on the basis of spectroscopic data, subsequent reactions, and the following considerations.

The cis ring juncture of **13** is suggested by previous observations that related pyrolyses lead preferentially to cis-fused ring systems;[9] in models of **11** it is virtually impossible to achieve the geometry necessary for trans cyclization. This stereochemistry of **13** was confirmed chemically by transformations noted below. The direct product expected[9,10] from this intramolecular ene reaction of the enol of **11** was the exo methylene ketone **13**, since previous cyclization of appropriately substituted cyclopentanones had furnished none of the alternative bicyclo[3.2.1]octanes.[12] The presence of **4** in the thermolysis product can be accounted for by wall-catalyzed[11] enolization of **13**, followed by symmetry-allowed[13] [1,5] hydrogen shift in the enol,[14] as shown in eq 2. Indeed we were able to carry out this rearrange-

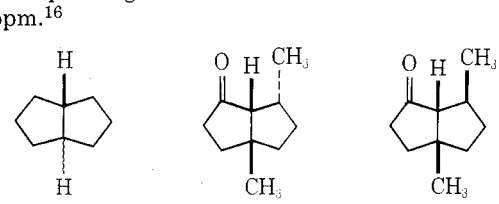


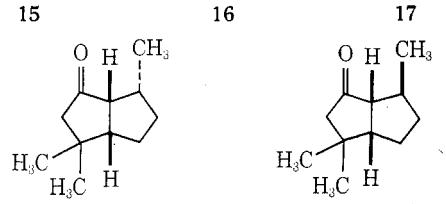
(2)

ment starting with purified **13**, and further to show that it is a reversible reaction. Thermolysis of either **4** or **13** at ~380° led to an equilibrium mixture containing these two isomers in the ratio 69:31 (**4**:**13**). Preparation of the strained skeleton of **4** was thus possible by this thermal route which permitted interconversion of **4** and **13** at a temperature sufficiently high to overcome what at room temperature presumably would be an unfavorable equilibrium. Furthermore, these thermal conditions quite specifically avoided in the final step the undesired presence of acid or base.

The expected sensitivity of **4** to enolizing conditions was confirmed. Exposure of the α,β-unsaturated ketone to potassium carbonate in aqueous alcohol at 80° led to smooth migration of the double bond out of conjugation and formation of **5**. At equilibrium the relative amounts of the two species are 3:97 (**4**:**5**). The equilibration was conveniently monitored spectroscopically, since the vestigial equilibrium concentration of **4** could be measured readily through its strong ultraviolet absorption at 261 nm (ϵ 8800). These measurements indicate that **4** is disfavored relative to **5** by about 2.4 kcal/mol. Since in **4** the double bond is both conjugated with the carbonyl group and also more highly substituted than in **5**, this energy difference must include some 2–3 kcal/mol stabilization for the disfavored isomer. With this fact taken into account, the estimated strain energy in **4** is approximately 5 kcal/mol, which appears quite reasonable. The corresponding difference, for example, between the cis and trans isomers of bicyclo[3.3.0]octane (**15**) as determined by calorimetry is 6.0 kcal/mol.[15]

This instability of trans-fused bicyclooctanes permits assignment of cis stereochemistry to **5**, since this β,γ-unsaturated ketone is formed under enolizing conditions. Catalytic hydrogenation of the double bond in either **5** or **13** gave rise to a mixture of the same two bicyclooctanones, **16** and **17**, and this correlation provides chemical evidence for the cis ring fusion in **13**. Addition of hydrogen to both **5** and **13** should be favored from the convex upper face of the molecule; on this basis the major hydrogenation product, which is the same in the two cases, is endo methyl ketone **16**. This stereochemical assignment is supported by NMR spectral comparisons between **16** and **17** and the previously described[16] ketones **18** and **19**. The doublet methyl signals in **16** and **17** appear at δ 1.00 and 1.12 ppm, respectively, while the corresponding resonances in **18** and **19** are at 1.0 and 1.11 ppm.[16]





Experimental Section

Materials and Equipment. All VPC was carried out using a Varian Aerograph Model A-90-P3 gas chromatograph with one of the following columns: A, 25% QF-1, 15 ft × 0.375 in.; B, 25% QF-1, 10 ft × 0.25 in.; C, 30% DEGS, 10 ft × 0.375 in.; D, 25% PDEAS, 50 ft × 0.25 in. All columns were prepared using 45/60 Chromosorb W in aluminum tubing. Uv spectra were obtained in 95% ethanol solutions with a Cary Model 14PM recording spectrophotometer. Ir and NMR spectra were obtained for CCl_4 solutions, the former on a Perkin-Elmer Model 237B spectrophotometer and the latter on a Varian HR-220 (220 MHz) spectrometer. Mass spectra were obtained on a Du Pont 21-492 double-focusing mass spectrometer with a resolution of 10^4 and results were processed with an AEI DS-30 data system. Boiling points are uncorrected; solutions were dried over $MgSO_4$. Unless otherwise noted, products were obtained as colorless oils.

3-(3-Butynyl)-3-methylcyclopentanone (11). The preparation of hydroxy ketal **6** has been described previously.[3] An analytical sample was obtained by preparative VPC on column B (160°, 120 ml/min): ir 3620 (m), 3475 (br), 2940 (s), 2855 (m), 1338 (m), 1100 (s), 1018 (s), 940 cm^{-1} (m); NMR δ 3.81 (s, 4 H), 3.29 (s, 2 H), 2.30 (br s, 1 H), 1.88–1.31 (m, 6 H), 1.04 (s, 3 H).

Anal. Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 62.61; H, 9.40.

Unpurified **6** (6.76 g, 39.3 mmol) in pyridine (100 ml) was converted to the tosylate with *p*-toluenesulfonyl chloride (11.45 g, 60 mmol) at 0° for 20 hr. The reaction mixture was poured onto ice and extracted three times with ether. The combined organic extracts were washed several times with water and then brine. After drying and removal of solvent in vacuo, 17.38 g (96%) of a pale red oil was obtained. An ir spectrum of this material lacked hydroxyl absorption and contained sulfonate ester bands at 1168 and 1177 cm^{-1}. Without further purification, the tosylate (1.265 g, 3.88 mmol) was treated with sodium iodide (4.92 g, 32.8 mmol) in hexamethylphosphortriamide (20 ml) at 75° for 20 hr. The reaction mixture was poured onto ice and extracted three times with pentane. The combined pentane extracts were washed with water and brine and dried. After removal of solvent by distillation through a Vigreux column and bulb-to-bulb distillation (105°, 0.6 mm), 993 mg (91%) of an oil was obtained: ir 2955 (s), 2880 (m), 1375 (m), 1330 (s), 1095 (s), 1023 (m), 932 cm^{-1} (m); NMR δ 3.79 (s, 4 H), 3.25 (s, 2 H), 1.95–1.50 (m, 7 H), 1.18 (s, 3 H). This crude iodo ketal (7.90 g, 29.1 mmol) was treated with lithio-1-trimethylsilylpropyne (2 equiv) for 2 hr at −25° according to the procedure of Corey.[5] Distillation of the crude product gave two major fractions, which were analyzed by ir spectroscopy and VPC on column C (167°, 135 ml/min). The first fraction (2.15 g), bp 78–95° (0.6 mm), was predominantly unprotected acetylenic ketal; the second fraction (2.49 g), bp 120–125° (0.6 mm), consisted essentially of the fully protected acetylene (70% yield).

Removal of both protecting groups was accomplished by treating an ethanolic solution of the distilled product with an equivalent weight of silver nitrate in 80% aqueous ethanol; after stirring at room temperature for 15 min, the reaction mixture was heated to reflux and then allowed to cool. Aqueous potassium cyanide (5 equiv) was added and the mixture was stirred for 1 hr. After dilution with water and extractive work-up with pentane, bulb-to-bulb distillation (135°, 12 mm) gave highly pure acetylenic ketone **11**. Spectra were recorded on a sample further purified by preparative VPC on column C (170°, 135 ml/min): ir 3310 (s), 2955 (s), 2115 (w), 1748 (s), 1400 (m), 1375 (w), 1245 (m), 1150 cm^{-1} (m); NMR δ 2.24–1.63 (m, 11 H), 1.07 (s, 3 H); mass spectrum *m/e* 150.1054 (M^+, calcd for $C_{10}H_{14}O$, 150.1044).

Longer reaction times and/or higher temperatures in the alkylation step produced significant amounts of internal acetylene, 3-(2-butynyl)-3-methylcyclopentanone, after deketalization. Separation was achieved by preparative VPC: ir 2958 (m), 2925 (w), 1747 (s), 1400 (m), 1375 (w), 1150 cm^{-1} (m); NMR δ 2.27–1.61 (m, 11 H) with t, J = 2.5 Hz, at 1.77, 1.13 (s, 3 H); mass spectrum *m/e* 150.1043 (M^+, calcd for $C_{10}H_{14}O$, 150.1044).

3-Butyl-3-methylcyclopentanone (12). To a suspension of copper iodide (15.24 g, 80 mmol) in anhydrous ether (300 ml), magnetically stirred under a nitrogen atmosphere and cooled to −25°, was added butyllithium (80 ml of a 2 *M* solution, 160 mmol) at a rate such that the temperature of the reaction did not exceed −20°. After completion of the addition, the mixture was stirred at −20 to −25° for 15 min before 3-methylcyclopent-2-enone (7.68 g, 80 mmol) in ether (50 ml) was added dropwise. After 0.5 hr at −25°, the reaction mixture was warmed to −5° and then poured

with rapid stirring onto saturated aqueous ammonium chloride. The ethereal layer was separated and the aqueous phase was extracted twice with ether; the combined organic phases were washed with saturated ammonium chloride, water, and brine and dried. Ir analysis of the residue obtained after removal of solvent in vacuo indicated no remaining unsaturated ketone. Purification was accomplished by distillation, bp 81–83° (10 mm), and preparative VPC on column C: ir 2960 (s), 2940 (s), 2875 (m), 2870 (m), 1748 (s), 1465 (m), 1400 (m), 1375 (m), 1250 (w), 1165 (m), 1125 cm^{-1} (m); NMR δ 2.22–2.12 (m, 2 H), 1.93 (AB q, J = 17.5 Hz, 2 H), 1.82–1.14 (m, 8 H), 1.04 (s, 3 H), 0.92 (t, J = 6.5 Hz, 3 H); mass spectrum m/e 154.1367 (M^+, calcd for $C_{10}H_{18}O$, 154.1357).

Hydrogenation of 11. The keto acetylene **11** was hydrogenated in methanol over 5% Pd/C. The reaction mixture was filtered, diluted with water, and extracted with pentane. After removal of solvent, the product had an identical VPC retention time and ir spectrum with those of authentic **12.**

Pyrolysis of 11. In general, 75–100 mg of the acetylenic ketone was placed in a 20-ml tube which was cooled, evacuated, sealed, and heated at ~380° for 7–10 min. Under these conditions, no acetylene remained. From 515 mg of **11** pyrolyzed in a number of batches, 483 mg was obtained after bulb-to-bulb distillation (115°, 12 min). VPC analysis on column A (158°) indicated the formation of a 1:1 mixture of two products. Preparative VPC gave a sample of each. The first was **13:** uv λ_{max} 294 nm (ϵ 99); ir 3070 (w), 2945 (s), 2860 (m), 1745 (s), 1645 (w), 1450 (m), 1410 (m), 1375 (w), 1240 (m), 1115 (m), 890 cm^{-1} (s); NMR δ 5.03 (dd, J = 2.0, 2.0 Hz, 1 H), 4.90 (dd, J = 2.0, 2.0 Hz, 1 H), 2.47 (br, 1 H), 2.46–2.22 (m, 4 H), 1.86–1.54 (m, 4 H), 1.22 (s, 3 H); mass spectrum m/e 150.1061 (M^+, calcd for $C_{10}H_{14}O$, 150.1044).

The second was **4:** uv λ_{max} 261 nm (ϵ 8800); ir 2945 (s), 2850 (m), 2825 (w), 1712 (s), 1655 (s), 1440 (m), 1415 (m), 1375 (m), 1295 (m), 1240 (m), 1118 (m), 1000 cm^{-1} (m); NMR δ 3.00–2.81 (m, 1 H), 2.59–2.27 (m, 3 H), 2.19–1.55 (m, 4 H), 1.97 (m, 3 H), 1.16 (s, 3 H); mass spectrum m/e 150.1047 (M^+, calcd for $C_{10}H_{14}O$, 150.1044).

Resubmission of either product to the reaction conditions for 1 hr produced an equilibrium mixture of 69% **4** and 31% **13.**

Base-Catalyzed Equilibration of 4. The α,β-unsaturated ketone **4** was taken up in 0.01 M potassium carbonate dissolved in 75% aqueous methanol (~1 mg/ml) and the mixture was heated at a gentle reflux under a nitrogen atmosphere for 1 day. After addition of water and extraction with pentane, VPC analysis of the residue on column A indicated one major (>90%) new peak which was collected and identified as **5:** uv λ_{max} 304 nm (ϵ 179); ir 3035 (w), 2945 (s), 2855 (m), 2845 (m), 1742 (s), 1448 (m), 1410 (m), 1375 (m), 1240 (m), 1015 (w), 840 cm^{-1} (w); NMR δ 5.43 (br s, 1 H), 2.47 (br s, 1 H), 2.32–2.14 (m, 4 H), 1.94–1.64 (m, 2 H), 1.71 (m, 3 H), 1.24 (s, 3 H); mass spectrum m/e 150.1040 (M^+, calcd for $C_{10}H_{14}O$, 150.1044).

The equilibration of **4** and **5** was performed in 95% ethanol and followed spectrophotometrically at 261 nm. The equilibrium constant for the reaction **4** $\rightleftarrows$ **5** is K = 32.3.

Preparation of *endo*- and *exo*-5,8-Dimethyl-*cis*-bicyclo[3.3.0]octan-2-one (16 and 17). Hydrogenation of **13** in methanol with 5% Pd/C catalyst gave a 22:78 mixture of two products. These were separated by preparative VPC on column D. First eluted was the minor product **17:** ir 2945 (s), 2855 (m), 1741 (s), 1455 (m), 1410 (w), 1375 (m), 1045 cm^{-1} (w); NMR δ 2.31–1.34 (br m, 10 H), 1.22 (s, 3 H), 1.12 (d, J = 6.5 Hz, 3 H); mass spectrum m/e 152.1201 (M^+, calcd for $C_{10}H_{16}O$, 152.1200).

Second eluted was the major product **16:** ir 2945 (s), 2855 (m), 1740 (s), 1450 (w), 1410 (w), 1375 (w), 1255 (w), 1140 cm^{-1} (m); NMR δ 2.31–1.34 (br m, 10 H), 1.21 (s, 3 H), 1.00 (d, J = 6.5 Hz, 3 H); mass spectrum m/e 152.1209 (M^+, calcd for $C_{10}H_{16}O$, 152.1200).

Hydrogenation of **5** under the same conditions produced **16** and **17** in the ratio 67:33.

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Registry No.—**1,** 694-73-5; **4,** 54931-37-2; **5,** 54931-38-3; **6,** 39859-28-4; **8,** 54931-39-4; **9,** 54931-40-7; **10,** 54931-41-8; **10** unprotected analog, 54931-42-9; **11,** 54931-43-0; **12,** 54931-44-1; **13,** 54931-45-2; **16,** 54931-46-3; **17,** 54931-47-4; 3-(2-butynyl)-3-methylcyclopentanone, 54931-48-5; 3-methylcyclopent-2-enone, 2758-18-1.

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