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Intramolecular Alkylations of Bicyclic α,β-Unsaturated Ketones[1]

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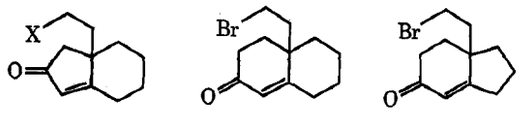
Bicyclic α,β-unsaturated ketones **1**, **2**, and **3**, having 2-bromoethyl groups as angular substituents, were prepared and their cyclizations by intramolecular alkylation investigated. High selectivities for α′-alkylation were found; tricyclic ketones **10**, **15**, and **17** were the major or sole products of cyclization.

Intramolecular alkylation of ketones is an attractive and popular synthetic route to polycyclic ketones. In most cases the synthetic scheme is designed such that only one mode of cyclization is possible. We here describe the intramolecular alkylations of a series of bicyclic α,β-unsaturated ketones (**1**, **2**, and **3**) in

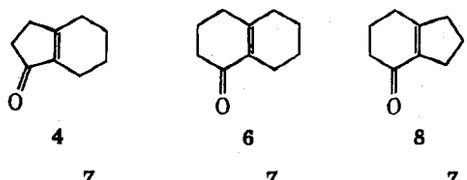


1a, X = Br
b, X = OMs

2 **3**

which, *a priori*, three possibilities for cyclization exist, *i. e.*, alkylation at the α position, at the γ position, or at the α′ position. Several examples of intramolecular alkylations of α,β-unsaturated ketones have been reported.[2-7] In some cases, the stereochemistry of the compound to be cyclized was such that only γ-alkylation was feasible;[2,3] however, in other cases in which competition among the several sites for alkylation seemed possible, selectivities for cyclization to the γ position[4,5] and to the α position[6,7] were observed.

The preparative route to ketones **1**, **2**, and **3** was based on Burgstahler's procedure for angular substitution[8] and the allylic oxidation method introduced by Dauben.[9] Thus, improvement[10] of the previously reported procedures for the conversion of **4** into **5a**[11] and **6** into **7a**[9] and extension to **8** to provide **9a** gave good yields of the angularly substituted bicyclic olefins.[12] Reduction of the aldehydes **5a**, **7a**, and **9a** gave the corresponding alcohols **5b**, **7b**, and **9b**, which were converted to the mesylates **5c**, **7c**, and **9c** and



4 **6** **8**

5 **7** **9**

a, Z = CHO
b, Z = CH_2OH
c, Z = CH_2OMs
d, Z = CH_2Br

treated with lithium bromide[13] to afford the bromo olefins **5d**, **7d**, and **9d**.[14] Oxidation[9] of the olefins with chromium trioxide–dipyridine complex, formed *in situ*,[15] provided the desired α,β-unsaturated ketones **1a**, **2**, and **3** (and **1b** from **5c**).

When cyclopentenone **1a** (or **1b**) was treated with potassium *tert*-butoxide in *tert*-butyl alcohol,[3] a mixture of ketones was obtained in which α,β-unsaturated ketone **10**, the product of α′-alkylation, and β,γ-unsaturated ketone **11**, the product of α-alkylation, were present in the ratio of 95:5. That the α,β-unsaturated ketone produced was **10** rather than **12**, the product of γ-alkylation, was demonstrated by catalytic reduction of the double bond to saturated ketone **13** followed by mild basic exchange of the active methylene hydrogens in methanol-*O*-*D*. The presence of only two exchangeable hydrogens confirmed the assignment of structures **13** and **10**; the saturated ketone **14**, derivable from **12**, would have had four exchangeable hydrogens.

(1) Presented in part at the 164th National Meeting of the American Chemical Society, New York, N. Y., Aug 1972, Abstracts, ORGN140.

(2) R. B. Bates, G. Büchi, T. Matsura, and R. R. Shaffer, *J. Amer. Chem. Soc.*, **82**, 2327 (1960). See also G. Büchi, W. Hofheinz, and J. V. Paukstelis *ibid.*, **91**, 6473 (1969).

(3) Intramolecular cyclization to the 4 position of the phenol can be considered γ-alkylation of an α,β-unsaturated ketone. For example, see S. Masamune, *ibid.*, **83**, 1009 (1961).

(4) (a) J. J. Bonet, H. Wehrli, and K. Schaffner, *Helv. Chim. Acta.*, **45**, 2615 (1962); (b) O. Halpern, P. Crabbe, A. D. Cross, I. Delfin, L. Cervantes, and A. Bowers, *Steroids*, **4**, 1 (1964).

(5) P. C. Mukharji and A. N. Ganguly, *Tetrahedron*, **25**, 5281 (1969).

(6) P. Grafen, H. J. Kabbe, O. Roos, G. D. Diana, Tsung-tee Li, and R. B. Turner, *J. Amer. Chem. Soc.*, **90**, 6131 (1968).

(7) C. Mercier, A. R. Addas, and P. Deslongshamps, *Can. J. Chem.*, **50**, 1882 (1972).

(8) A. W. Burgstahler and I. C. Nordin, *J. Amer. Chem. Soc.*, **83**, 198 (1961).

(9) W. G. Dauben, M. Lorber, and D. S. Fullerton, *J. Org. Chem.*, **34**, 3587 (1969).

(10) Longer reaction times in formation of the vinyl ethers of the allylic alcohols obtained upon reduction of **4**, **6**, and **8** resulted in much improved yields.

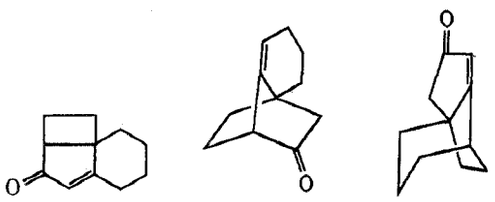
(11) (a) R. L. Cargill and A. M. Foster, *J. Org. Chem.*, **35**, 1971 (1970); (b) A. M. Foster, Ph.D. Thesis, University of South Carolina, Columbia, S. C., 1970.

(12) Attempts to convert the alcohol obtained from **4** into the methyl ester corresponding to **5a** by the orthoacetate method [W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, Tsung-tee Li, D. J. Faulkner, and M. R. Petersen, *J. Amer. Chem. Soc.*, **92**, 741 (1970)] failed owing to elimination from the allylic alcohol, which is unstable to storage.

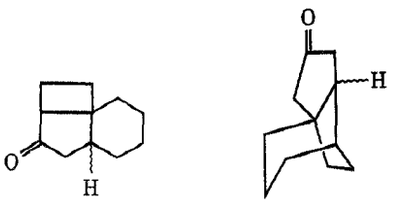
(13) J. W. Cornforth, R. H. Cornforth, and K. K. Mathew, *J. Chem. Soc.*, 2539 (1959).

(14) The bromides were preferred to the mesylates owing to easier purification of the bromo olefins and bromo enones.

(15) R. Ratcliffe and R. Rodehurst, *J. Org. Chem.*, **35**, 4000 (1970).

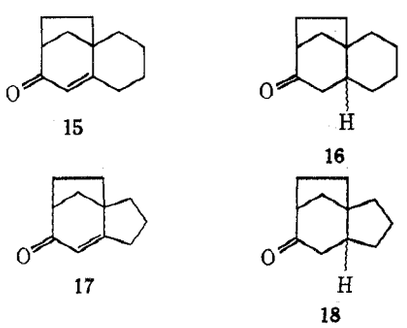


10 11 12



13 14

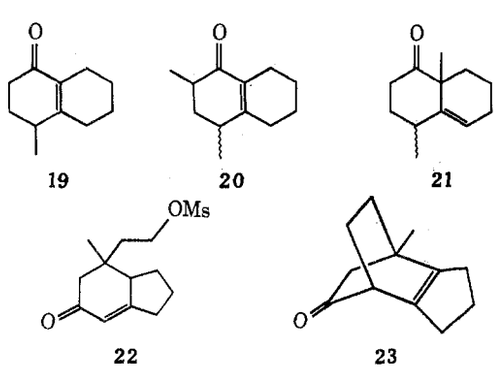
The selectivity for α'-alkylation found with the cyclopentenone increased to the point of specificity with the cyclohexenones. Similar cyclization of cyclohexenone **2** gave α,β-unsaturated ketone **15**, which was reduced to saturated ketone **16** having two ex-



15 16 17 18

changeable hydrogens; cyclohexenone **3** yielded α,β-unsaturated ketone **17**, which was converted to saturated ketone **18** with two exchangeable hydrogens.

That the kinetically formed enolate anion of such α,β-unsaturated ketones is the α' anion and the conjugated α (or γ) anion is the more stable anion has been demonstrated.[16] Thus, treatment of the kinetically formed enolate anion of **19** with methyl iodide resulted in formation of **20**, the product of α'-alkylation, but the equilibrated anion yielded **21**, the product of α-alkylation. This suggests that the selectivities noted in the intramolecular alkylations might result from trapping of the kinetically formed α'-enolate anion; however, this does not seem to be the best explanation. The use of equilibrating conditions for the cyclizations, the isolation of β,γ-unsaturated



19 20 21 22 23

(16) P. S. Wharton and E. C. Sundin, *J. Org. Chem.*, **33**, 4255 (1968). See also G. Stork and J. Benaim, *J. Amer. Chem. Soc.*, **93**, 5939 (1971).

ketone **11**, and the recent report[7] that the major product of cyclization of cyclohexenone **22** under equilibrating conditions was β,γ-unsaturated ketone **23** argue against trapping of the kinetically formed anion. Examination of appropriate models in each case (including **23**) indicates that the observed product is the least strained of those possible. The products obtained from **1**, **2**, **3**, and **22** result from the lowest energy transition state available for intramolecular alkylation of an equilibrating mixture of α' and extended enolate anions.

Experimental Section

Microanalyses were performed by Bernhardt Microanalytisches Laboratorium, Elbach uber Engelskirchen, West Germany. Melting points and boiling points are uncorrected. Analytical gas–liquid partition chromatography (glpc) was carried out on an Aerograph Model 1200 Hy-FI employing 3% SE-30, 8 ft × 0.125 in.; 3% DEGS, 8 ft × 0.125 in.; 3% DC-710, 8 ft × 0.125 in.; and 10% Carbowax 1000, 6 ft × 0.125 in. columns. Preparative glpc was carried out on an Aerograph Model A-90-P3 using a 20% SE-30, 5 ft × 0.25 in. column. Silica gel used for column chromatography was E. Merck 0.05–0.20 mm silica gel. The following spectrometers were used: uv, Perkin-Elmer 202; ir, Perkin-Elmer 337 and 257; nmr, Varian A-60 and XL-100; mass spectrum, Hitachi RM-U6D. Generally, only absorptions important for characterization or identification and particularly strong absorptions are reported.

6-(2-Hydroxyethyl)bicyclo[4.3.0]non-1(9)-ene (5b).—Bicyclo[4.3.0]non-1(6)-en-7-one (**4**)[17] (26.2 g, 192 mmol) in dry ether (473 ml) under a drying tube was cooled in an ice–water bath and lithium aluminum hydride (6.2 g, 164 mmol) was added to the stirred solution. The ice bath was removed and the mixture was stirred at room temperature for 1 hr before it was again cooled with an ice–water bath and treated with H_2O (6.2 ml), 15% NaOH (6.2 ml), and H_2O (18.6 ml). After an additional 1 hr of stirring, the white precipitate was filtered and washed a few times with ether. The combined ethereal solution was dried ($MgSO_4$) and concentrated *in vacuo* to give bicyclo[4.3.0]non-1(6)-en-7-ol[12] as a clear oil (26.0 g, 98%) which had the expected ir spectrum[11] and was used at once for vinyl ether formation. The freshly prepared alcohol (26.0 g, 188 mmol) in ethyl vinyl ether (1.2 l.) (freshly distilled from sodium hydride) under N_2 was treated with mercuric acetate (15.0 g) (recrystallized from absolute ethanol containing 1% glacial acetic acid), and the resulting solution was heated under reflux for 57 hr. Glacial acetic acid (0.74 ml) was added, and reflux was continued for an additional 3 hr. The cooled reaction mixture was diluted to 1750 ml with pentane, washed with 5% NaOH (500 ml), dried (K_2CO_3), and concentrated *in vacuo* to a yellow oil (40 g) which was immediately washed through a column of Alcoa F-20 alumina (300 g) with pentane. Combination of the fractions containing the desired ether gave bicyclo[4.3.0]non-1(6)-en-7-yl vinyl ether (22.2 g, 71.5%) with ir and nmr spectra identical with those reported.[11] A portion of this vinyl ether (21.3 g, 130 mmol) was stirred while N_2 was bubbled through it for 1 hr; then the flask was equipped with an uncooled condenser and an N_2 bubbler and placed in an oil bath. The oil bath was warmed to 190° during 15 min. When the bath temperature reached 185°, a brief period of gas evolution caused foaming, which was controlled by cooling the condenser. After 1 hr at 190°, the oil was allowed to cool to room temperature, giving bicyclo[4.3.0]non-1(9)-ene-6-acetaldehyde (**5a**) (20.8 g, 97.7%) with the expected spectral characteristics.[11] A portion of the aldehyde (20.3 g, 124 mmol) in dry ether (473 ml) under a drying tube was cooled in an ice–water bath and treated with lithium aluminum hydride (4.7 g, 124 mmol). The bath was removed and the reaction mixture was stirred at room temperature for 70 min before it was again cooled with an ice–water bath and treated successively with H_2O (4.7 ml), 15% NaOH (4.7 ml), and H_2O (14.1 ml). Work-up in the usual way gave the alcohol **5b** (17.6 g, 86%) as an oil

(17) The preparation of **4** from cyclohexene and acrylic acid using polyphosphoric acid (PPA) [S. Dev, *J. Indian Chem. Soc.*, **34**, 169 (1957)] is limited in scale owing to the difficulty in stirring the viscous PPA mixture. Substitution of methanesulfonic acid containing phosphorus pentoxide [P. E. Eaton and R. H. Mueller, *J. Amer. Chem. Soc.*, **94**, 1014 (1972), footnote 11] for PPA allows easy scale-up and affords purer product.

containing only traces of impurities by glpc: ir (CCl_4) 3300, 3040, 2940, 2870, 1450 cm^{-1}; nmr ($CDCl_3$) δ 5.20 (m, 1), 3.60 (t, 2, J = 7 Hz), 1.0–2.5 (m, 15). An analytical sample was obtained by preparative glpc.

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.38; H, 10.75.

6-(2-Bromoethyl)bicyclo[4.3.0]non-1(9)-ene (5d).—The above alcohol **5b** (12.50 g, 75.2 mmol) in dry pyridine (50 ml) under a drying tube was cooled in an ice–water bath and treated with methanesulfonyl chloride (7 ml, 11.5 g, 100 mmol). After a few minutes of stirring, a large amount of precipitate formed. The bath was removed and the mixture was kept at room temperature for 0.5 hr before H_2O (2 ml) was carefully added. The resulting mixture was taken up in ether–water. After the phases were separated and the aqueous phase was back-washed with ether, the combined ethereal solution was washed with 3 N HCl (five times, until the washings remained strongly acidic), H_2O, saturated $NaHCO_3$ (twice), and saturated NaCl, dried ($MgSO_4$), and concentrated *in vacuo* to give **5c** (14.63 g, 80%) as a yellowish oil: ir (CCl_4) 3020, 2920, 2840, 1370, 1350, 1170, 950 cm^{-1}; nmr ($CDCl_3$) δ 5.2 (m, 1), 4.13 (m, 2), 2.95 (s, 3), 1.0–2.5 (m, 14). The mesylate (14.6 g, 60.0 mmol) was dissolved in acetone (60 ml), treated with anhydrous lithium bromide (15.55 g, 180 mmol), and heated at reflux under a drying tube for 3 hr.[13] The cooled reaction mixture was diluted with acetone; then the solid was filtered and washed with acetone. The combined acetone solution was concentrated *in vacuo* to an oil which was taken up in ether–water. After the phases were separated, the ether solution was washed with water, saturated $NaHCO_3$, and saturated NaCl, dried ($MgSO_4$), and concentrated *in vacuo* to give the bromide **5d** as an orange liquid (12.2 g) which was vacuum distilled to give two fractions which were pure by glpc [(1) bp 62–64° (0.2 mm), 2.52 g; (2) bp 69–73° (0.15 mm), 8.76 g (combined yield 11.28 g, 82% from **5c**, 66% from **5b**)]: ir (CCl_4) 3020, 2910, 2830, 1450, 1215 cm^{-1}; nmr ($CDCl_3$) δ 5.22 (m, 1), 3.25 (m, 2), 1.0–2.5 (m, 14). An analytical sample was obtained by preparative glpc.

Anal. Calcd for $C_{11}H_{17}Br$: C, 57.65; H, 7.48; Br, 34.87. Found: C, 57.61; H, 7.37; Br, 34.83.

6-(2-Bromoethyl)bicyclo[4.3.0]non-1(9)-en-8-one (1a).[9]—To the burgundy colored solution[15] resulting from the addition of CrO_3 (20 g, 200 mmol = 300 mmol [O]) (ground and dried over P_2O_5 in a vacuum desiccator) to an ice–water bath cooled solution of pyridine (32.2 ml, 400 mmol) (distilled from BaO) in CH_2Cl_2 (500 ml) (distilled from P_2O_5) under N_2 with 15 min stirring (mechanical stirrer, blade in top of liquid) was added the bromo olefin **5d** (5.01 g, 21.8 mmol) in CH_2Cl_2 (10 ml). The ice–water bath was removed and the mixture was stirred for 17.5 hr before CH_2Cl_2 (250 ml), pyridine (16.1 ml, 200 mmol), and CrO_3 (10.0 g, 100 mmol = 150 mmol [O]), successively, were added.[18] After an additional 7 hr of stirring, the CH_2Cl_2 solution was decanted, the solid residue was washed several times with CH_2Cl_2, and the combined CH_2Cl_2 solution was washed with saturated $NaHCO_3$ (four times). Concentration *in vacuo* gave an oil which was taken up in ether (500 ml). The ether solution was washed with saturated $NaHCO_3$ (twice), H_2O, 3 N HCl (twice), H_2O, saturated $NaHCO_3$, and saturated NaCl before it was dried ($MgSO_4$) and concentrated *in vacuo* to a yellow liquid (4.39 g). Chromatography over silica gel (102 g) (1:1 hexane–ether) followed by recrystallization (ether–hexane) of the combined fractions containing bromo ketone gave crystalline **1a** (3.09 g, 58%) in several crops. Further recrystallization of a sample for spectra and analysis gave **1a**: mp 55.5–56.5°; uv max (95% EtOH) 233 nm (ϵ 13,300); ir (CCl_4) 2915, 2840, 1710, 1625, 1450, 1225, 855 cm^{-1}; nmr ($CDCl_3$) δ 5.80 (m, 1), 3.15 (m, 2), 1.1–2.7 (m, 12).

Anal. Calcd for $C_{11}H_{15}BrO$: C, 54.34; H, 6.22; Br, 32.86. Found: C, 54.25; H, 6.02; Br, 32.84.

Cyclization of 1a.[19]—The bromo ketone **1a** (1.000 g, 4.12 mmol) under Ar was dissolved in dry *tert*-butyl alcohol (40 ml) and treated with 1 M potassium *tert*-butoxide in *tert*-butyl alcohol (5 ml). A white precipitate formed at once in the clear solution. The stirred suspension was heated at gentle reflux for 22 hr,[20] allowed to cool, and poured into pentane–saturated NaCl. After the phases were separated, the aqueous phase was back-washed with pentane, and the combined pentane solution was washed several times with saturated NaCl, H_2O, and saturated NaCl, dried ($MgSO_4$), and concentrated by distillation of the pentane to give the product as a pale yellow liquid (0.300 g, 45%). Examination by glpc (assuming equal response factors) showed the presence of two components in a ratio of *ca.* 95:5; spectra indicated that the major product was an α,β-unsaturated ketone and the minor product a nonconjugated ketone. For separation of the components, the product was chromatographed over a column of silica gel (30 g), using 9:1 hexane–ethyl acetate to remove the ketones. First collected was the less polar tricyclo[5.2.2.$0^{1,6}$]undec-5-en-9-one (**11**) (16 mg, 2.4%): ir (CCl_4) 2990 (weak), 2915, 1755, 1705 cm^{-1} (weak); nmr ($CDCl_3$) δ 5.47 (t, 1, J = 7.5 Hz), 2.85 (m, 1), 1.2–2.2 (m, 12); mass spectrum (20 eV) m/e (rel intensity) 162 (14), 120 (100), 118 (61). Second was collected the more polar α,β-unsaturated ketone tricyclo[7.2.0.$0^{4,9}$]undec-3-en-2-one (**10**) (281 mg, 42.2%). A sample of this ketone collected by glpc for spectra and analysis had uv max (95% EtOH) 236 nm (ϵ 13,200); ir (CCl_4) 2910, 2830, 1695, 1450, 1440, 1170, 870 cm^{-1}; nmr ($CDCl_3$) δ 5.90 (finely split s, 1), 1.2–2.9 (m, 13).

Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.42; H, 8.77.

Structure determination of the α,β-unsaturated ketone was carried out by hydrogenation of 187 mg (1.15 mmol) in ethyl acetate (6 ml) with 10% Pd/C (13 mg) as catalyst at ambient temperature and pressure. When hydrogenation (1 equiv of H_2) was complete, the catalyst was filtered with the aid of Celite, and the resulting solution was concentrated to give the saturated ketone tricyclo[7.2.0.$0^{4,9}$]undecan-2-one (**13**)[21] as a clear oil (184 mg, 97%). A portion collected by glpc for spectra and analysis had ir (CCl_4) 2905, 2840, 1740, 1450 cm^{-1}; nmr ($CDCl_3$) δ 2.5–1.1 (m, 16); mass spectrum (70 eV) m/e (rel intensity) 164 (22), 136 (100).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.08; H, 9.63.

The number of active hydrogens was determined by base-catalyzed exchange. A portion of saturated ketone **13** (30.5 mg) was dissolved in a solution of $NaOCH_3$ in CH_3OD (1 ml) (prepared by addition of a small piece of sodium to CH_3OD). After 1.5 hr at room temperature the solvent was removed *in vacuo*, and the residue was taken up in D_2O–ether. After separation of the phases and further extraction of the D_2O with ether, the combined ethereal solution was dried (K_2CO_3) and concentrated *in vacuo* to a clear oil (29.8 mg). Examination by nmr showed a decrease in intensity of some, but not all, of the signals in the region δ 2.1–2.5. Analysis by mass spectroscopy and comparison with the mass spectrum of the untreated saturated ketone showed the product of exchange contained 7 mol % $C_{11}H_{16}O$, 32 mol % $C_{11}H_{15}DO$, 61 mol % $C_{11}H_{14}D_2O$, no $C_{11}H_{13}D_3O$, and no $C_{11}H_{12}D_4O$. The presence of only two exchangeable hydrogens confirmed that the α,β-unsaturated ketone was **10**.

6-(2-Hydroxyethyl)bicyclo[4.4.0]decene (7b).—Bicyclo[4.4.0]-dec-1(6)-en-2-one (**6**) was converted to the alcohol and the vinyl ether in the same manner described above for **4**. The vinyl ether (8.3 g) was stirred under aspirator vacuum until all bubbling ceased, then for an additional 1 hr, Ar was bubbled through the stirred liquid for 0.5 hr, and the liquid was again stirred under vacuum until gas evolution ceased. The resulting liquid, stirred under N_2 under an uncooled short-path (Alembic) still, was heated to 190° during 5 min and stirred at that temperature for 0.5 hr with a slight amount of foaming. The resulting product was a clear oil (7.1 g, 86%) (73% from **6**) having the infrared spectrum expected for **7a**.[8] The crude aldehyde **7a** (7.1 g, 40 mmol) was reduced with $LiAlH_4$ (1.0 g, 26 mmol) as previously described for **5a**; the crude product (7.4 g, 103%) was a clear, colorless oil containing a few droplets of another phase and two significant impurities by glpc (possibly from the starting material). For spectra and analysis, a sample of pure alcohol **7b** was collected by glpc as a clear oil: ir (CCl_4) 3590, 3300 (broad), 3020, 2910,

(18) This second addition of oxidant[9] is necessary; in preliminary experiments, oxidation of **5d** to **1a** and of **5c** to **1b** without the second addition of oxidant resulted in *ca.* 20% remaining unoxidized starting material.

(19) Similar results were obtained on cyclization of crude **1b**.[14] When **1a** containing *ca.* 20% **5d**[18] was cyclized in a preliminary experiment, the **5d** was recovered unchanged; thus elimination (which would require removal of a proton from a neopentyl-type carbon) does not occur significantly under these conditions.

(20) Further experiments with the cyclohexenones indicated that the period of reflux is unnecessary.

(21) The stereochemistry of the angular hydrogen introduced upon hydrogenation of the double bond is unassigned owing to lack of evidence; for the structural assignments this information is unimportant.

2840, 1450, 1050, 1040 cm^{-1}; nmr ($CDCl_3$) δ 5.35 (m, 1), 3.63 (t, 2, J = 7.5 Hz), 1.3–2.1 (m, 17).

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18; Found: C, 79.86; H, 11.28.

6-(2-Bromoethyl)bicyclo[4.4.0]dec-1-ene (7d).—The crude alcohol **7b** (7.3 g, 40 mmol) was treated with methanesulfonyl chloride in pyridine as described for the conversion of **5b** to **5c**. The crude mesylate **7c**, obtained as a clear oil (8.0 g, 31 mmol, 78%) with ir (CCl_4) 2920, 2840, 1370, 1350, 1170, 940 cm^{-1}, was treated with lithium bromide in acetone as described for the preparation of **5d**. The crude bromide **7d** was obtained as a red oil (6.5 g, 80%). Analysis by glpc showed the same two impurities present in the alcohol and new, minor ones. Samples for spectra and analysis were collected by glpc giving **7d** as a clear oil: ir (CCl_4) 2910, 2840, 1450 cm^{-1}; nmr ($CDCl_3$) δ 5.38 (m, 1), 3.30 (m, 2), 1.1–2.3 (m, 16).

Anal. Calcd for $C_{12}H_{19}Br$: C, 59.27; H, 7.88; Br, 32.86. Found: C, 59.16; H, 7.98; Br, 32.77.

6-(2-Bromoethyl)bicyclo[4.4.0]dec-1-en-3-one (2).—By the procedure described for the preparation of **1a**, the crude bromide **7d** (6.3 g, 26 mmol) was oxidized to the bromo enone **2**. Chromatography of the crude product, a yellow oil (4.6 g), over silica gel using mixtures of hexane and ethyl acetate, followed by recrystallization (hexane–ether) of the fractions containing **2**, gave white, crystalline **2** (1.26 g, 19%) and an uncrystallized yellow oil (0.48 g, 7%) of essentially pure **2**. A sample of **2** further recrystallized for spectra and analysis was a white, crystalline solid: mp 51.5–52°; uv max (95% EtOH) 241 nm (ϵ 14,000); ir (CCl_4) 2920, 2850, 1680, 1625, 1465, 1330, 860 cm^{-1}; nmr ($CDCl_3$) δ 5.75 (finely split s, 1), 3.3 (m, 2), 1.2–2.6 (m, 14).

Anal. Calcd for $C_{12}H_{17}BrO$: C, 56.02; H, 6.67; Br, 31.09. Found: C, 55.81; H, 6.89; Br, 30.88.

Cyclization of 2.—A portion of crystalline **2** (287 mg, 1.12 mmol) under Ar was dissolved in dry *tert*-butyl alcohol (12 ml) and treated with 1 *M* potassium *tert*-butoxide in *tert*-butyl alcohol (2 ml). A white precipitate formed at once in the reaction mixture, which was stirred at 35–40° for 6.5 hr before it was worked up as described for the cyclization of **1a**. Examination of the crude product, a slightly yellow oil (153 mg, 78%), by glpc and ir showed the only product to be tricyclo[7.2.1.0^{4,9}]dodec-3-en-2-one (**15**). Spectra of **15** were obtained from the product of a different preparation, and purified by passage through a column of silica gel (9:1 hexane–ethyl acetate) and preparative glpc, giving **15** as a clear oil: uv max (95% EtOH) 244 nm (ϵ 11,900); ir (CCl_4) 3020, 2940, 2860, 1680, 1610, 1450, 1260 cm^{-1}; nmr ($CDCl_3$) δ 5.58 (m, 1) 2.80 (m, 1), 1.2–2.6 (m, 14). An analytical sample was prepared by filtration of the product of the above described preparation through a small column of silica gel (1:1 hexane–ether) followed by collection from glpc.

Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.64; H, 8.98.

Catalytic hydrogenation of **15** as described for the conversion of **10** to **13** gave tricyclo[7.2.1.0^{4,9}]dodecan-2-one (**16**)[21] as a colorless oil: ir (CCl_4) 2920, 2850, 1710, 1450 cm^{-1}; nmr ($CDCl_3$) δ 2.63 (m, 1), 1.0–2.4 (m, 17); mass spectrum (70 eV) *m/e* (rel intensity) 178 (67), 41 (100).

Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.74; H, 10.03.

Although the structural assignments for **15** and **16** were clear from the spectra (*i.e.*, bridgehead proton α to ketone at δ 2.63 in **16**), the deuterium exchange experiment was carried out as before, resulting in a product mixture containing 3 mol % $C_{12}H_{18}O$, 19 mol % $C_{12}H_{17}DO$, 78 mol % $C_{12}H_{16}D_2O$, no $C_{12}H_{15}D_3O$, and no $C_{12}H_{14}D_4O$ and confirming the structural assignments.

Bicyclo[4.3.0]non-1-ene-6-acetaldehyde (9a).—By procedures similar to those described previously, bicyclo[4.3.0]non-1(6)-en-2-one (**8**)[22] (9.43 g, 69.4 mmol) was converted successively into the alcohol [ir (CCl_4) 3580, 3400 cm^{-1} (broad)[1]] (8.8 g, 63.7 mmol, 92%), the vinyl ether [ir (CCl_4) 3100, 2920, 2825, 1630, 1610 cm^{-1}; nmr ($CDCl_3$) δ 6.32 (d of d, 1, J = 14 Hz, J = 7.5 Hz), 4.27 (d of d, 1, J = 14 Hz, J = 1.5 Hz), 4.22 (m, 1), 3.92 (d of d, 1, J = 7.5 Hz, J = 1.5 Hz), 1.5–2.6 (m, 12)] (8.22 g, 50 mmol, 78.5%), and the aldehyde **9a** [7.14 g, 43.5 mmol (87%); 63% from **8**]. Pure **9a** collected by glpc was a clear oil: ir (CCl_4) 2920, 2825, 2710, 1720 cm^{-1}; nmr ($CDCl_3$) δ 9.70 (t, 1, J = 3 Hz), 5.37 (m, 1), 1.2–2.6 [m, 14, including 2.35 (d, 2, J = 3 Hz)].

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.09; H, 9.80.

6-(2-Hydroxyethyl)bicyclo[4.3.0]non-1-ene (9b).—Reduction of **9a** (6.82 g, 41.5 mmol) (containing an impurity from the rearrangement) as described for the similar aldehydes gave **9b** (5.82 g, 78%) (still containing the impurity). A purer sample of **9b** (from another preparation) had ir (CCl_4) 3590, 3300 (broad), 3020 (weak), 2910, 1450, 1043 cm^{-1}; nmr ($CDCl_3$) δ 5.3 (m, 1), 3.60 (t, 2, J = 7.5 Hz), 2.68 (s, 1), 1.0–2.5 (m, 14). An analytical sample was collected from glpc.

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.41; H, 10.92.

6-(2-Bromoethyl)bicyclo[4.3.0]non-1-ene (9d).[23]—The above described crude alcohol **9b** (5.33 g, 32 mmol) and a small amount of *o*-phenanthroline were dissolved in ether (100 ml) under Ar. The solution was cooled to 0° with an isopropyl alcohol–Dry Ice bath and treated with methyllithium (14 ml of 1.9 *M* solution, 27 mmol) at 0° until the reaction mixture became a coffee-colored suspension. The suspension was then treated at −10 to 0° with methanesulfonyl chloride (2.3 ml, 30 mmol). The bath was removed and the suspension was allowed to warm to room temperature before it was treated with anhydrous lithium bromide (8.7 g, 100 mmol) and allowed to stir for 21 hr. The reaction mixture was poured into saturated $NaHCO_3$. After phases were separated, the ether solution was washed with water and saturated $NaHCO_3$, dried (K_2CO_3), and concentrated *in vacuo* to give crude **9d** as an orange oil (6.78 g, 92.5%). Examination by glpc showed that the impurity present in **9a** and **9b** (retention time 0.8 min) remained as essentially the only impurity in **9d** (retention time 3.2 min). The impurity was removed by distillation at room temperature under high vacuum, using a Dry Ice cooled alembic still. The resulting **9d** (5.07 g), containing *ca.* 3% impurity, had ir (CCl_4) 3040, 2940, 2870, 2840, 1455, 1440 cm^{-1}; nmr ($CDCl_3$) δ 5.3 (m, 1), 3.2 (m, 2), 1.0–2.5 (m, 14). An analytical sample was obtained by glpc.

Anal. Calcd for $C_{11}H_{17}Br$: C, 57.65; H, 7.48; Br, 34.87. Found: C, 57.47; H, 7.44; Br, 34.81.

6-(2-Bromoethyl)bicyclo[4.3.0]non-1-en-3-one (3).[24]—By the procedure described for the preparation of **1a** and **2**, the above described bromide **9d** (2.05 g, 8.95 mmol) was converted into enone **3**. The crude product (1.4 g) was chromatographed over silica gel (50 g), using mixtures of hexane–ethyl acetate, yielding a pure fraction of **3** (491 mg, 24%) as an oil which resisted attempts at crystallization, and which cyclized to **17** upon injection into the glpc instrument. The bromo enone **3** was thus characterized as an oil: uv max (95% EtOH) 240 nm; ir (CCl_4) 2950, 2870, 1675, 1630 cm^{-1}; nmr ($CDCl_3$) δ 5.77 (m, 1), 3.43 (t, 2, J = 8.5 Hz), 1.2–2.8 (m, 12); mass spectrum (70 eV) *m/e* (rel intensity) 244 (6), 242 (6), 216 (21), 214 (21), 202 (8), 200 (8), 163 (42), 79 (100).

Cyclization of 3.—A portion of **3** (273 mg, 1.12 mmol) under Ar was dissolved in dry *tert*-butyl alcohol (20 ml) and treated with 1 *M* potassium *tert*-butoxide in *tert*-butyl alcohol (2 ml). A precipitate formed at once. After 15 min of stirring, the reaction mixture was worked up as described for the cyclizations of **1a** and **2**. The crude product (83 mg, 46%) was a yellow oil which was found to contain tricyclo[6.2.1.0^{4,8}]undec-3-en-2-one (**17**) as the only ketone present. Purification over a column of silica gel (1:1 hexane–ether) gave pure **17** (75 mg, 41%) as a clear oil. For spectra and analysis, **17** collected by glpc was a clear oil: uv max (95% EtOH) 242 nm (ϵ 11,700); ir (CCl_4) 2940, 2850, 1670, 875 cm^{-1}; nmr ($CDCl_3$) δ 5.7 (m, 1), 1.2–3.0 (m, 13); mass spectrum (70 eV) *m/e* (rel intensity) 162 (30), 134 (18), 121 (100).

Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.28; H, 8.82.

Catalytic hydrogenation of **17** as previously described gave tricyclo[6.2.1.0^{4,8}]undecan-2-one (**18**)[21] as a clear oil: ir (CCl_4) 2950, 2860, 1710 cm^{-1}; nmr ($CDCl_3$) δ 2.63 (m, 1), 1.1–2.5 (m,

(22) An improved procedure for the preparation of **8** results from use of methanesulfonic acid–phosphorus pentoxide (see footnote 17) instead of PPA, which is used in the previously described preparation: R. K. Hill and R. T. Conley, *J. Amer. Chem. Soc.*, **82**, 645 (1960). More convenient purification of the product is afforded by distillation, bp 43° (0.10 mm).

(23) When the procedure used for the preparation of **5d** from **5b** and **7d** from **7b** was applied to **9b**, a mixture of **5d** and **9d** was obtained, apparently as a result of isomerization of **9c** in the work-up procedure. The procedure used for preparation of **9d** is a better and more convenient one for this transformation of alcohol to bromide.

(24) For a synthesis of the 2-acetoxyethyl compound corresponding to **3**, see N. P. Peet and R. L. Cargill, *J. Org. Chem.*, **38**, 1215 (1973).

15); mass spectrum (70 eV) *m/e* (rel intensity) 164 (42), 41 (100). An analytical sample was prepared by glpc.

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.01; H, 9.77.

Again the shift (δ 2.63) of the bridgehead hydrogen adjacent to the ketone in **18** confirmed the structural assignment, but the deuterium experiment was carried out, giving a product containing 3 mol % $C_{11}H_{16}O$, 14 mol % $C_{11}H_{15}DO$, 83 mol % $C_{11}H_{14}D_2O$, no $C_{11}H_{13}D_3O$, and no $C_{11}H_{12}D_4O$ and confirming the structural assignments.

Registry No.—**1a**, 39837-99-5; **2**, 39832-73-0; **3**, 39832-74-1; **4**, 22118-00-9; **5a**, 24097-40-3; **5b**, 39832-76-3; **5c**, 39832-77-4; **5d**, 39832-78-5; **6**, 18631-96-4; **7a**, 39832-80-9; **7b**, 39832-81-0; **7c**, 39832-82-1; **7d**, 39832-83-2; **8**, 22118-01-0; **9a**, 39832-85-4; **9b**, 39832-86-5; **9d**, 39832-87-6; **10**, 39832-88-7; **11**, 39832-89-8; **13**, 24736-69-4; **15**, 39832-91-2; **16**, 39832-92-3; **17**, 39832-93-4; **18**, 39832-94-5; bicyclo[4.3.0]non-1(6)-en-7-ol, 39832-95-6; bicyclo[4.3.0]non-1(6)-en-7-yl vinyl ether, 39832-96-7; methanesulfonyl chloride, 124-63-0.

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The Synthesis of α-Branched Ketones from Dihydro-1,3-oxazines *via* the Ketenimine Intermediate. α-Substituted Ketones from a Stable Ketenimine[1]

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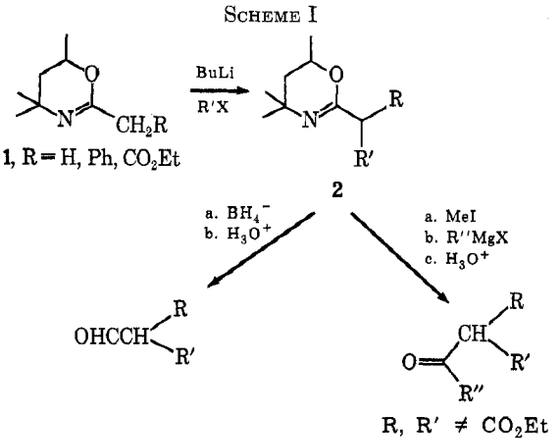
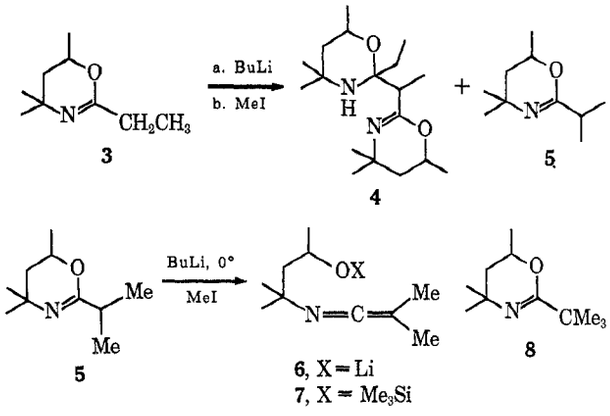
The tertiary proton abstraction from 2-isoalkyloxazines (**12**) by organolithiums leads to rapid ketenimine rearrangement. The ketenimines are shown to be useful precursors to a variety of highly substituted ketones by virtue of successive alkylations. The ketenimine intermediate was verified by isolation as its trimethylsilyl ether (**7**) and also used as a precursor to substituted ketones by addition of Grignard or organolithium reagents.

The readily available tetramethyldihydro-1,3-oxazine **1** (R = H) has been shown to serve as a useful precursor to aldehydes[4] and ketones[5] by the equations set forth in Scheme I. In addition, the corresponding

SCHEME I



2-benzyl (R = Ph) and 2-carboethoxy (R = CO_2Et) derivatives led to substituted oxazines by virtue of alkylation of their respective carbanions. These, in turn, were transformed into carbonyl compounds by similar manipulations. Among the limitations noted for these methods[4,5] was the failure of oxazines possessing *n*-alkyl (**1**, R = Me, Et, Pr, etc.) or isoalkyl (**2**, R, R′ = Me, Et, etc.) substituents to form a stable carbanion capable of further alkylation. For example, the 2-ethyloxazine **3** gave mainly the dimer **4** upon treatment with butyllithium (or other comparable bases) and methyl iodide under a variety of conditions. The expected product **5** was produced in only 10–15% yield. Similar treatment of the 2-isopropyloxazine **5** indicated complete inertness to strong base below ~0°; yet above this temperature (0–25°) it was rapidly transformed into the ketenimine **6**. The latter was trapped by addition of trimethylchlorosilane and **7** was isolated in 35–40% yield. Only a trace of the 2-*tert*-butyloxazine **8** was found among the product. It is evident,



therefore, that secondary and tertiary carbanions α to the oxazine ring are unstable to the temperatures at which they are formed, rearranging to open-chain ketenimines which react further with nucleophiles present. This oxazine–ketenimine rearrangement thus prohibits the synthesis of α-alkylaldehydes *via* Scheme I but was deemed sufficiently novel that a study to assess its potential was undertaken.[6]

(1) Part XX of a study on the chemistry of dihydro-1,3-oxazines. For previous papers in this series see A. I. Meyers and N. Nazarenko, *J. Org. Chem.*, **38**, 175 (1973).

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(4) A. I. Meyers, A. Nabeya, H. W. Adickes, I. R. Politzer, G. R. Malone, A. C. Kovelesky, R. L. Nolen, and R. C. Portnoy, *J. Org. Chem.*, **38**, 36 (1973).

(5) A. I. Meyers and E. M. Smith, *J. Org. Chem.*, **37**, 4289 (1972).

(6) The synthesis of α-alkylaldehydes was accomplished, nevertheless, using the 2-vinyloxazine and successive addition of Grignard reagent and alkyl iodides (see ref 4).