Conformational Effect on the Bridgehead Reaction of Bicyclo[3.3.1]nonan-2-ones. A Facile Bridgehead Deuteration of a Bicyclo[3.3.1]nonan-2-one Derivative with the Cyclohexanone Ring Locked in the Boat Conformation

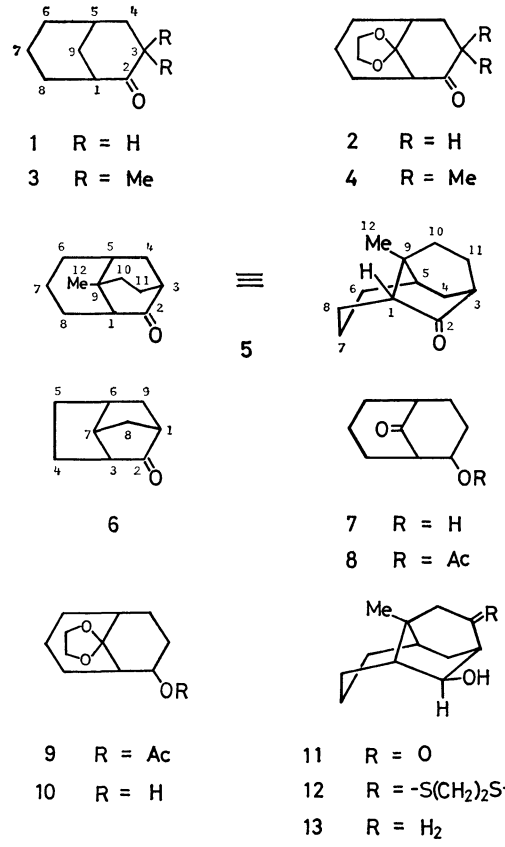
Kiyoyuki YAMADA,* Shunichi MANABE, Yoshinori KYOTANI,
Masaaki SUZUKI, and Yoshimasa HIRATA
Department of Chemistry, Faculty of Science, Nagoya University, Chikusa, Nagoya 464

(Received July 3, 1978)

Five bicyclo[3.3.1]nonan-2-ones, two known (**1**, **3**) and three new ones (**2**, **4**, **5**) were prepared. The hydrogen-deuterium exchange reaction at the bridgehead position of the bicyclo[3.3.1]nonan-2-one system was examined under mild basic conditions (2 M NaOMe–MeOD, 33 °C, 22 h) using these five bicyclo[3.3.1]-nonan-2-ones. Virtually no deuteration took place at the bridgehead in each case of the bicyclic ketones (**1**, **2**, **3**, **4**), whereas one deuterium was incorporated into the bridgehead of the ketone (**5**). ^{13}C NMR spectroscopy was employed for the unambiguous determination of the site(s) of deuteration in all cases studied. The enhanced bridgehead acidity of (**5**) could be explained in terms of the locked boat conformation of the cyclohexanone ring contained in (**5**).

Schaefer and Lark[1] observed in 1965 that deuteration of the bridgehead position of bicyclo[3.3.1]nonan-2-one (**1**) occurred under basic conditions (*e.g.*, 77.2% deuteration: 0.1 M NaOD–D_2O, 95 °C, 40 days), and discussed the importance of the boat conformation of the ketone-bearing ring for stabilization of the bridgehead enolate. In 1975, Nickon and his coworkers[2] demonstrated that the bridgehead acidity of brendan-2-one (**6**) possessing the boat-locked bicyclo[3.2.1]-octan-2-one system was largely enhanced, resulting in the hydrogen-deuterium exchange at C-3 in **6** under mild conditions (92% deuteration: 4.84 M NaOD in MeOD, 25 °C, 69 h). Further they revealed that the enhanced bridgehead acidity of **6** was neither due to the "s" character of the carbon in the bridgehead C–H nor due to inductive stabilization of the carbanion by the carbonyl, but due to the facile formation of the corresponding enolate, which could be rationalized in terms of the Wiseman's postulate.[3]

We herein describe our results on the hydrogen-deuterium exchange reaction at the bridgehead position of the bicyclo[3.3.1]nonan-2-one system under the basic conditions milder than those[1] of Schaefer and Lark. The bicyclo[3.3.1]nonan-2-ones employed in the present studies are **1**, **2**, **3**, **4**, and **5**, among which the last one is a 4-homoisotwistane derivative and contains the cyclohexanone ring held rigidly in the boat conformation by the two-carbon bridge. The two known compounds, **1**[4] and **3**[6] were prepared by the modified procedures of Cope and his coworkers[5] and of Marvell and his colleagues,[6] respectively. Other three new compounds (**2**, **4**, **5**) were synthesized as follows. The acetal ketone (**2**) was synthesized from a diastereomeric mixture (*exo*-ol:*endo*-ol, 7:4) of the keto alcohol (**7**)[5] by the following sequence: (i) acetylation to give the keto acetate (**8**); (ii) acetalization affording the acetal acetate (**9**); and (iii) alkaline hydrolysis to yield the acetal alcohol(**10**) and subsequent oxidation (chromium trioxide–pyridine). Methylation of **2** with methyl iodide–sodium hydride in 1,2-dimethoxyethane gave the ketone (**4**). The tricyclic ketone (**5**) was synthesized from the keto alcohol (**11**),[7] which was converted to the corresponding thioacetal alcohol (**12**). Desulfurization of **12** with Raney nickel afforded the alcohol (**13**), oxidation of which with chromium trioxide in pyridine gave the tricyclic ketone (**5**) (The numbering system shown in **5**, although it differs from that based on the IUPAC rule, is used in the present paper for convenience of comparing ^{13}C chemical shifts with those of other bicyclo[3.3.1]nonan-2-ones).



Bridgehead Hydrogen Exchange. The hydrogen-deuterium exchange reaction for each of the bicyclo-[3.3.1]nonan-2-ones (**1**, **2**, **3**, **4**, **5**) was carried out in deuteriomethanol in the presence of sodium methoxide (2.0 M NaOMe–MeOD) at 33 °C for 22 h, and the extent of deuteration was determined by mass spectrometry.[8] The results are summarized in Table 1. The location of the deuterium(s) in each product was

Table 1. Deuterium incorporation by bicyclo-[3.3.1]nonan-2-ones
(2.0 M NaOMe-MeOD at 33 °C for 22 h)

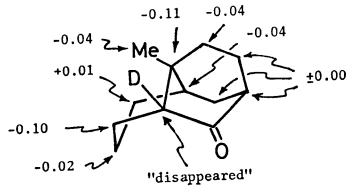
Compound	Mass spectral d assay (rel %±1)[a]			
	d_0	d_1	d_2	d_3
1	33	45	19	3
2	30	44	23	3
3	97	3		
4	100	0		
5	5	95		

a) Average of five mass spectral scans; corrected for ^{13}C.

proved by ^{13}C NMR spectroscopy (*cf.* Table 2). Most of the ^{13}C NMR chemical shift assignments for the bicyclo[3.3.1]nonan-2-ones, shown in Table 2, were made by the application of chemical shift theory[9-11] and single frequency off-resonance decoupling (sford) experiments, and further in some cases [in particular in **5**] with the aid of deuterium isotope shifts[12-15] and comparisons with structurally related compounds.[15,16] Although assignments of some signals remained uncertain for each compound (Table 2), there was no ambiguity as to the determination of the site(s) of deuteration.

Under the present exchange conditions the ketone (**2**) was shown to incorporate up to 2 equivalents of deuterium (**2**-d_1 44% and **2**-d_2 23%), the site of deuteration being shown to be C-3 as expected (*vide post*), and the incorporation of deuterium into the bridgehead position (C-1) was found to occur to an extremely small extent (3%). The site of deuteration in **2** was proved by the deuterium isotope effects in proton-noise decoupled ^{13}C NMR spectra:[12-14] on deuteration of **2** the singlet at δ 37.99 (C-3) was shifted upfield by 0.32 ppm to become a triplet due to ^{13}C–D coupling (J_{C-D}=19.6 Hz), and the singlet at δ 23.73 (C-4) was broadened and shifted upfield by *ca.* 0.06 ppm. The result on the deuteration of the ketone (**1**) was virtually the same as that of the ketone (**2**) (see Table 1). The ketone (**3**), which possesses the gem dimethyl groups at C-3, was deduced to have the different conformation(s) regarding the cyclohexanone ring from that of the ketone (**1**). It was thus expected that the ketone (**3**) might exhibit reactivity at the bridgehead different from that of **1**. However, there was no significant incorporation of deuterium into the ketone (**3**) under the exchange conditions. No deuterium was incorporated into the bridgehead of the ketone (**4**) which has the gem dimethyl groups at C-3.

In contrast to the bicyclic compounds, **3** and **4**, the ketone (**5**) was found to be monodeuterated (95% d_1), and further it was established by ^{13}C NMR spectroscopy (*vide post*) that the deuterium was located at the bridgehead position (C-1) of **5**, excluding the possibility of deuteration by the mechanism of homoenolization.[13] It is known that homoenolization can only be effected under conditions (*e.g.*, *t*-BuOK–*t*-BuOH, 185 °C, 150 h) much more vigorous than those employed in the present studies. In the ^{13}C NMR spectrum of the monodeuterated compound (**5**-d_1) the signal at δ 52.28 assigned to the bridgehead (C-1) apparently disappeared. The ^{13}C chemical shift differences between **5**-d_1 and **5** [δ(**5**-d_1)−δ(**5**)] are shown in **5A**, and these magnitudes



5A

Table 2. ^{13}C chemical shifts of bicyclo[3.3.1]nonan-2-ones[a,b]

Carbon	**1**	**2**	**3**	**4**	**5**	**5**-d_1
1	45.06 (d)	54.65 (d)	42.89 (d)	53.17 (d)	52.28 (d)	"disappeared"
2	217.06 (s)	213.73 (s)	220.28 (s)	221.22 (s)	221.89 (s)	221.89 (s)
3	39.08 (t)	37.99 (t)	42.89 (s)	41.74 (s)	43.40 (d)	43.40 (d)
4	27.43 (t)	23.70 (t)	40.95 (t)	39.98 (t)	29.39 (t)	29.39 (t)
5	26.16 (d)	35.41 (d)	26.50 (d)	36.61 (d)	35.04 (d)	35.00 (d)
6	31.95 (t)[c]	30.47 (t)[c]	35.00 (t)[c]	31.85 (t)[c]	24.69 (t)	24.70 (t)
7	20.12 (t)	18.76 (t)	19.40 (t)	18.31 (t)	16.68 (t)	16.66 (t)
8	29.79 (t)[c]	27.45 (t)[c]	32.81 (t)[c]	30.08 (t)[c]	24.02 (t)	23.92 (t)
9	32.55 (t)[c]	109.77 (s)	29.52 (t)[c]	109.48 (s)	34.13 (t)	34.02 (s)
10					33.40 (t)	33.36 (t)
11					27.92 (t)	27.92 (t)
Ketal CH_2		64.23 (t)		64.18 (t)		
Ketal CH_2		64.50 (t)		64.33 (t)		
3-Me			26.77 (q)	29.06 (q)		
3-Me			31.28 (q)	32.77 (q)		
9-Me					23.00 (q)	22.96 (q)

a) Spectra taken in $CDCl_3$ at 20 MHz on a Varian CFT-20 spectrometer; chemical shifts are in parts per million relative to tetramethylsilane. b) The letter in parentheses refers to the signal multiplicity obtained from single frequency off-resonance decoupling experiments: s=singlet, d=doublet, t=triplet, q=quartet. c) Assignments may be interchanged among these signals in each vertical column.

of the upfield shifts for sp^3 carbons both geminal and vicinal to deuterium are in good agreement with those reported for deuterated 4-homoisotwistanes,[15] which has the same carbon skeleton as **5**, and for some bicyclic compounds[12c,12d,13,14] (*e.g.*, isotope shifts of carbons geminal to deuterium, 0.12 ± 0.04 ppm[12c]). Further some signals in the ^{13}C NMR spectrum of the deuterated ketone (**5**-d_1) were shown to be broadened by geminal (C-8 and C-9) and vicinal (C-5, C-7, C-10, and C-12) ^{13}C–D couplings. Thus the site of deuteration in **5** was proved to be C-1. It should be noted in this case that the ^1H NMR spectral analysis was not a reliable method of determining the deuterated site of **5**, because the signal due to H-1 could not unambiguously be identified.

Among the five bicyclo[3.3.1]nonan-2-ones (**1**, **2**, **3**, **4**, **5**) examined, the ketone (**5**) was a sole member that underwent deuteration at the bridgehead position under the exchange conditions of the present studies. As in the case of brendan-2-one (**6**),[2] the enhanced bridgehead acidity of **5** would be ascribed to the locked boat conformation of the cyclohexanone ring, in which the dihedral angle between the C(1)–H bond and the p-orbital of the carbonyl carbon is as small as *ca.* 30° from the examination of Dreiding models: this small value of the dihedral angle between the interacting orbitals would not only be favorable for removal of the proton at C-1 but result in the stabilization of the bridgehead enolate formed. On the other hand, the ketonic ring is conformationally flexible in each of the bicyclic analogs (**1**, **2**, **3**, **4**). Under the exchange conditions the flexible ketonic ring presumably can not assume the genuine boat conformation like that in **5** owing to the steric compression within the molecule, but exist as an another conformer such as a deformed boat (or as an equilibrium mixture of conformers other than boat), in which the dihedral angle discussed above is not so small as that (*ca.* 30°) in **5**, making removal of the bridgehead proton more difficult.

From the present studies it is concluded that the bicyclo[3.3.1]nonan-2-one system with the ketonic ring kept rigidly in the boat form shows the enhanced bridgehead acidity in comparison with that possessing the conformationally flexible ketonic ring.

Experimental

Melting points and boiling points are uncorrected. IR spectra were taken with a JASCO Model IRS or JASCO DS-402G spectrometer in $CHCl_3$. ^1H-NMR spectra were obtained in $CDCl_3$ using a Varian HA-100D (100 MHz) or NV-21 (90 MHz) instrument: chemical shifts (δ) are reported in ppm downfield from internal TMS. ^{13}C-NMR spectra were obtained in $CDCl_3$ (concentration, 0.3—0.4 mmol/ml) on a Varian CFT-20 spectrometer operating 20 MHz in the Fourier transform mode: chemical shifts are given in relative to internal TMS. Low resolution mass spectra were determined on a Hitachi RMU-6C mass spectrometer equipped with a heating inlet system as well as a direct inlet system and operating with an ionization energy of 70 eV. High resolution mass spectra were determined on a JEOLCO GMS-01SG mass spectrometer. Silica gel 60 F_{254} (No. 5715) and 60 PF_{254} (No. 7747) (E. Merck, A. G., Germany) were used for TLC: thickness employed was 1.50 mm for preparative TLC. Organic solutions were washed with saturated NaCl solution, dried over anhydrous Na_2SO_4, and evaporated by a vacuum rotary evaporator.

*Bicyclo[3.3.1]nonan-2-one (**1**).* A solution of a diastereomeric mixture (*exo*-ol:*endo*-ol, 4:7) of the keto alcohol (**7**)[5] (350 mg) and $BF_3\cdot OEt_2$ (0.15 ml, distilled from CaH_2) in *1,2*-ethanedithiol (5 ml) was stirred at room temperature for 40 min and diluted with ether (150 ml). The mixture was washed with 5 M NaOH (5×6 ml) and water (6 ml), and dried. On evaporation of the solvent there remained a colorless oil, which was purified by preparative TLC ($CHCl_3$–EtOAc, 3:1), giving 510 mg (98%) of a diastereomeric mixture of the thioacetal alcohol as a colorless liquid: IR 3460 cm^{-1}; ^1H-NMR (90 MHz) 3.10—3.50 (4H, complex m), 4.04 and 4.41 (total 1H, m each); MS 230 (M^+). To a solution of the diastereomeric mixture of the thioacetal alcohol (510 mg) in EtOH (12 ml) was added W-2 Raney nickel (*ca.* 8 g). The suspension was refluxed for 40 min and filtered. The filtrate was evaporated, affording a solid, which was purified by preparative TLC ($CHCl_3$–EtOAc, 3:1), affording a diastereomeric mixture of the alcohol (299 mg, 96%) as a colorless solid: IR 3650 cm^{-1}; ^1H-NMR (90 MHz) 3.60 and 3.90 (total 1H, m each); MS 140 (M^+). Found: *m/e* 140.1212. Calcd for $C_9H_{16}O$: 140.1201. A suspension of CrO_3 (420 mg) in dry pyridine (11 ml) was added to a cooled (0 °C) solution of the diastereomeric mixture of the alcohol (299 mg) in dry pyridine (3.6 ml) with stirring. The mixture was stirred at room temperature for 12 h and diluted with ether (250 ml). The precipitates were filtered through a pad of Super Cel and washed with ether thoroughly. The combined filtrates were washed with 2 M HCl and water, dried, and concentrated. Purification of the oily residue by preparative TLC ($CHCl_3$) gave **1** (160 mg, 54%) as colorless crystals: mp 127—132 °C (sealed tube) (lit, mp 135—137 °C[17] and 129—137 °C[4b]); IR 1695 cm^{-1}; ^1H-NMR (100 MHz) 2.40—2.70 (3H, complex m); MS 138 (M^+). Found: *m/e* 138.1052. Calcd for $C_9H_{14}O$: 138.1045.

*3,3-Dimethylbicyclo[3.3.1]nonan-2-one (**3**).* A solution of **1** (185 mg, 1.34 mmol) in dry 1,2-dimethoxyethane (DME, 1.1 ml) was added to a stirred suspension of NaH [250 mg of 55% mineral oil dispersion (*ca.* 4.5 mmol), three times washed with dry hexane and dried *in vacuo*] in dry DME (5.6 ml) under nitrogen. Methyl iodide (1.67 ml, 26.6 mmol) was added to the suspension, and the mixture stirred at room temperature for 26 h. After an excess amount of NH_4Cl was added, the mixture was concentrated, cooled (0 °C), diluted with water (4 ml), and extracted with $CHCl_3$ (3×10 ml). The combined $CHCl_3$ extracts were washed with water (3 ml), dried, and evaporated, giving a residue, purification of which by preparative TLC ($CHCl_3$) afforded **3** (104 mg, 47%) as a colorless liquid: IR 1686 cm^{-1}; ^1H-NMR (90 MHz) 1.12 (3H, s), 1.17 (3H, s), 2.44 (1H, m); MS 166 (M^+). Found: *m/e* 166.1361. Calcd for $C_{11}H_{18}O$: 166.1358.

*9-Oxobicyclo[3.3.1]non-2-yl Acetate (**8**).* A solution of a diastereomeric mixture (*exo*-ol:*endo*-ol, 4:7) of the keto alcohol (**7**)[5] (150 mg) in acetic anhydride (1.2 ml) and dry pyridine (2.9 ml) was stirred at room temperature for 12 h, and concentrated. The residue was purified by preparative TLC ($CHCl_3$–EtOAc, 5:1) to give the diastereomeric mixture of **8** (188 mg, 98%) as a colorless liquid: bp 178—181 °C/1 mmHg; IR 1733, 1723 cm^{-1}; ^1H-NMR (90 MHz) 2.01 and 2.06 (total 3H, s, each), 5.11 and 5.33 (total 1H, m each); MS 196 (M^+). Found: *m/e* 196.1085. Calcd for $C_{11}H_{16}O_3$: 196.1099.

9,9-Ethylenedioxybicyclo[3.3.1]non-2-yl Acetate (9). To a solution of the diastereomeric mixture of **8** (198 mg) in toluene (7 ml) were added *p*-toluenesulfonic acid monohydrate (7 mg) and ethylene glycol (0.9 ml). The stirred mixture was refluxed for 4 h using a Dean-Stark water separator to remove the water. After cooling, the mixture was washed with saturated $NaHCO_3$ solution (5 ml), dried, and concentrated. The residue was purified by preparative TLC ($CHCl_3$–EtOAc, 5:1), affording the diastereomeric mixture of **9** (234 mg, 97%) as a colorless liquid: IR 1723 cm^{-1}; ^{1}H-NMR (90 MHz) 2.04 (3H, s), 3.80—4.30 (4H, complex m), 5.01 and 5.25 (total 1H, m each); MS 240 (M^+). Found: *m/e* 240.1366. Calcd for $C_{13}H_{20}O_4$: 240.1362.

9,9-Ethylenedioxybicyclo[3.3.1]nonan-2-ol (10). To a solution of the diastereomeric mixture of **9** (234 mg) in tetrahydrofuran (THF, 5.8 ml) was added a mixture of H_2O (1.2 ml)–10% NaOH (1.6 ml)–MeOH (5.8 ml). The mixture was stirred at room temperature for 40 min and passed through a column of ion-exchange resin (H form, Amberlite CG-50 Type-I) (3.5 g). The column was further washed with MeOH (20 ml) for complete elution of the product. The combined mixtures were concentrated and the residue was dissolved in EtOH (30 ml). The solution was evaporated to give a residue, purification of which by preparative TLC ($CHCl_3$–EtOAc, 7:1) yielded the diastereomeric mixture of **10** (191 mg, 99%) as a colorless liquid: IR 3580, 3500 (broad) cm^{-1}; ^{1}H-NMR (90 MHz) 3.70—4.10 (4H, m, A_2B_2 type), 3.90 and 4.20 (total 1H, m each); MS 198 (M^+). Found: *m/e* 198.1247. Calcd for $C_{11}H_{18}O_3$: 198.1256.

9,9-Ethylenedioxybicyclo[3.3.1]nonan-2-one (2). To a stirred solution of the diastereomeric mixture of **10** (191 mg) in dry pyridine (2.9 ml) was added under cooling (0 °C) a suspension of CrO_3 (260 mg) in dry pyridine (7.1 ml) in one portion. The mixture was stirred at room temperature for 13 h, diluted with ether (150 ml), and filtered through a pad of Super Cel. The solid residue was washed with ether (40 ml). The combined filtrates were washed with water repeatedly until the washing became colorless, dried, and concentrated. The residue was purified by preparative TLC ($CHCl_3$–EtOAc, 7:1), giving **2** (160 mg, 85%) as a colorless liquid: IR 1700 cm^{-1}; ^{1}H-NMR (100 MHz) 3.95 (4H, s); MS 196 (M^+). Found: *m/e* 196.1108. Calcd for $C_{11}H_{16}O_3$: 196.1099.

9,9-Ethylenedioxy-3,3-dimethylbicyclo[3.3.1]nonan-2-one (4). To a stirred suspension of NaH [276 mg of 55% mineral oil dispersion (*ca.* 5 mmol), three times washed with dry hexane and dried *in vacuo*] in dry DME (6.1 ml) was added a solution of **2** (290 mg, 1.48 mmol) in dry DME (1.2 ml) under nitrogen. To the suspension MeI (1.84 ml, 29.3 mmol) was added, and the mixture stirred at room temperature for 29 h. An excess amount of NH_4Cl was added and, after 10 min, the mixture was concentrated. The residue was cooled, diluted carefully with water (5 ml), and extracted with $CHCl_3$ (4×10 ml). The combined $CHCl_3$ extracts were washed with water (5 ml), dried, and concentrated to afford an oily residue, purification of which by preparative TLC ($CHCl_3$) yielded **4** (164 mg, 50%) as colorless crystals: mp 54—56 °C; IR 1685 cm^{-1}; ^{1}H-NMR (90 MHz) 1.20 (3H, s), 1.24 (3H, s), 2.47 (1H, m), 3.93 (4H, s); MS 224 (M^+). Found: *m/e* 224.1408. Calcd for $C_{13}H_{20}O_3$: 224.1412.

Tricyclic Thioacetal Alcohol (12). A mixture of the crystalline keto alcohol (**11**)[7] (179 mg) and $BF_3 \cdot OEt_2$ (0.1 ml, distilled from CaH_2) in *1,2*-ethanedithiol (4 ml) was stirred at room temperature for 30 min, and diluted with saturated $NaHCO_3$ solution (5 ml) under cooling (0 °C). The mixture was extracted with $CHCl_3$ (4×10 ml). The combined $CHCl_3$ extracts were dried and concentrated. The residue was dissolved in toluene and the solution evaporated: this procedure was repeated for complete removal of *1,2*-ethanedithiol present in the residue. The resulting residue was purified by preparative TLC ($CHCl_3$–EtOAc, 8:1), giving the tricyclic thioacetal alcohol (**12**) (268 mg, 97%) as colorless crystals: mp 77—78 °C; IR 3400 (broad) cm^{-1}; ^{1}H-NMR (90 MHz) 0.90 (3H, s), 3.20—3.70 (4H, m, A_2B_2 type), 4.05 (1H, m); MS 270 (M^+). Found: *m/e* 270.1120. Calcd for $C_{14}H_{22}OS_2$: 270.1112.

Tricyclic Alcohol (13). A suspension of **12** (265 mg) and W-2 Raney nickel (*ca.* 4 g) in EtOH (25 ml) was refluxed for 45 min and filtered. The filtrate was concentrated to afford **13** (176 mg, 99%) as colorless crystals: mp 145—147 °C (sealed tube); IR 3660, 3440 (broad) cm^{-1}; ^{1}H-NMR (90 MHz) 0.87 (3H, s), 3.85 (1H, broad s); MS 180 (M^+). Found: *m/e* 180.1497. Calcd for $C_{12}H_{20}O$: 180.1514.

Tricyclic Ketone (5). Under cooling (0 °C) a suspension of CrO_3 (247 mg) in dry pyridine (6.2 ml) was added to a stirred solution of **13** (210 mg) in dry pyridine (2.8 ml) at one time. The mixture was stirred at room temperature for 13 h, diluted with ether (80 ml), and filtered through a pad of Super Cel. The solid residue was washed with ether repeatedly. The combined filtrates were washed with 1.5 M HCl (4×15 ml) and water (4×10 ml), dried, and concentrated. The resulting oily residue was purified by preparative TLC ($CHCl_3$) to yield the tricyclic ketone (**5**) (170 mg, 82%) as colorless crystals: mp 130—133 °C (sealed tube; sublimed at 40 °C/20 mmHg); IR 1714 cm^{-1}; ^{1}H-NMR (90 MHz) 1.01 (3H, s), 1.87 (1H, m), 2.34 (1H, m); MS 178 (M^+). Found: *m/e* 178.1353. Calcd for $C_{12}H_{18}O$: 178.1358.

Deuterium Exchange Reaction. In each run a ketone (0.05—0.5 mmol) was dissolved in a 2.0 M NaOMe solution in MeOD (≥99%, CEA, France) containing 9.4 molar equivalents of NaOMe and the solution was stirred at 33 °C for 22 h under nitrogen. The exchange reaction was repeated at least twice for each ketone, and it was confirmed that the extent of deuteration was reproducible. An example of the representative procedure follows. A solution of the ketone (**5**) (12.8 mg, 0.072 mmol) in 0.34 ml (0.68 mmol of NaOMe) of 2.0 M NaOMe in MeOD was stirred at 33 °C for 22 h under nitrogen, and then diluted with 1 ml of D_2O (≥99.75%, CEA, France). The mixture was extracted with hexane (4×8 ml). The combined organic extracts were washed with D_2O (5 ml), dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by preparative TLC ($CHCl_3$), affording 9.4 mg (74%) of pure **5** as colorless crystals. The sample was analyzed for deuterium content by mass spectrometry.

References

1) J. P. Schaefer and J. C. Lark, *J. Org. Chem.*, **30**, 1337 (1965).

2) A. Nickon, D. F. Covey, F. Huang, and Y-N. Kuo, *J. Am. Chem. Soc.*, **97**, 904 (1975).

3) a) J. R. Wiseman, *J. Am. Chem. Soc.*, **89**, 5966 (1967); b) J. R. Wiseman and W. A. Pletcher, *J. Am. Chem. Soc.*, **92**, 956 (1970).

4) a) E. N. Marvell, D. Sturmer, and C. Rowell, *Tetrahedron*, **22**, 861 (1966); b) J. P. Schaefer, J. C. Lark, C. A. Flegal, and L. M. Honig, *J. Org. Chem.*, **32**, 1372 (1967).

5) A. C. Cope, D. L. Nealy, P. Scheiner, and G. Wood, *J. Am. Chem. Soc.*, **87**, 3130 (1965).

6) E. N. Marvell, G. J. Gleicher, D. Sturmer, and K. Salisbury, *J. Org. Chem.*, **33**, 3393 (1968).

7) K. Yamada, M. Aratani, Y. Hayakawa, H. Nakamura, H. Nagase, and Y. Hirata, *J. Org. Chem.*, **36**, 3653 (1971).
8) K. Biemann, "Mass Spectrometry, Organic Chemical Applications," McGraw-Hill, New York (1962), Chap. 5.
9) G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists," Wiley-Interscience, New York (1972).
10) J. B. Stothers, "Carbon-13 NMR Spectroscopy," Academic Press, New York (1972).
11) G. E. Maciel in "Topics in Carbon-13 NMR Spectroscopy," ed by G. C. Levy, Wiley-Interscience, New York (1974), Vol. 1, Chap. 2.
12) a) G. L. Lebel, J. D. Laposa, B. G. Sayer, and R. A. Bell, *Anal. Chem.*, **43**, 1500 (1971); b) R. A. Bell, C. L. Chan, and B. G. Sayer, *J. Chem. Soc., Chem. Commun.*, **1972**, 67; c) J. B. Stothers, C. T. Tan, A. Nickon, F. Huang, R. Sridhar, and R. Weglein, *J. Am. Chem. Soc.*, **94**, 8581 (1972); d) D. H. Hunter, A. L. Johnson, J. B. Stothers, A. Nickon, J. L. Lambert, and D. F. Covey, *J. Am. Chem. Soc.*, **94**, 8582 (1972); e) H. N. Colli, V. Gold, and J. E. Pearson, *J. Chem. Soc., Chem. Commun.*, **1973**, 408; f) A. P. Tulloch and M. Mazurek, *J. Chem. Soc., Chem. Commun.*, **1973**, 692; g) A. L. Johnson, J. B. Stothers, and C. T. Tan, *Can. J. Chem.*, **53**, 212 (1975); h) A. P. Tulloch, *Can. J. Chem.*, **55**, 1135 (1977).
13) J. B. Stothers in Ref. 11, Chap. 6.
14) N. K. Wilson and J. B. Stothers in "Topics in Stereochemistry," ed by E. L. Eliel and N. L. Allinger, Wiley-Interscience, New York (1974), Vol. 8.
15) Y. Fujikura, K. Aigami, N. Takaishi, H. Ikeda, and Y. Inamoto, *Chem. Lett.*, **1976**, 507.
16) K. M. Majerski, Z. Majerski, and E. Pretsch, *J. Org. Chem.*, **41**, 686 (1976).
17) J. P. Ferris and N. C. Miller, *J. Am. Chem. Soc.*, **85**, 1325 (1963).