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Reaction of Lithioisobutyrophenone with (+)-2(*S*)-Iodooctane in Weakly Polar Aprotic Solvents

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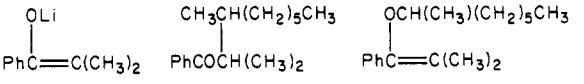
Lithioisobutyrophenone reacts with (+)-2(*S*)-iodooctane to give the corresponding enol ether **3** and 1-phenyl-2,2,3-trimethylnonanone (**2**), together with 1- and 2-octenes. In dimethoxyethane and dioxolane, the C- and O-alkylation products are formed in the ratios 0.56 and 0.85, respectively, with net inversion of configuration. These products are partially racemized, but this appears to be due to concomitant racemization of 2-iodooctane by iodide rather than a significant substitution pathway involving retention. Optically pure (+)-1-phenyl-2,2,3(*R*)-trimethylnonanone has been synthesized in eight steps from (+)-(*R*)-pulegone.

Introduction

It is generally believed that the alkylations of phenolate and enolate ions by primary and secondary alkyl halides and tosylates in weakly polar solvents occur by the S_N2 mechanism.[1,2] There are, however, several reports[3-5] that indicate that, while O-alkylation probably takes place with complete inversion as expected for this mechanism, C-alkylation is much less stereospecific and may occur in part by a mechanism involving retention of the center undergoing nucleophilic substitution. Okamoto and his co-workers[5] have made a careful study of the alkylation of sodium phenolate by primary ([1-^{2}H]butyl) and secondary alkyl halides in several solvents and have found appreciable racemization during the formation of the *o*-alkylphenols in contrast to the para isomers and alkyl phenyl ethers that appear to be formed with complete inversion of the asymmetric center undergoing substitution. Earlier, Suama et al.[4] reported that C-alkylation of the enolate salts of methyl acetoacetate and acetylacetone by 2-butyl bromide in the polar solvent dimethyl sulfoxide occurs with partial net retention of configuration, whereas O-alkylation proceeds with net inversion. Because of concomitant racemization of the 2-butyl bromide, it was not possible to establish whether O-alkylation involved complete inversion, but the stereospecificity of this latter process was considerably higher than that for C-alkylation.

Bram, Welvart, and co-workers[6] have examined the analogous reaction of methyl sodioacetoacetate with 2-octyl bromide, iodide, and tosylate. Under phase-transfer conditions, C-alkylation occurred with net inversion, which was, however, significantly less than the degree of inversion for competing O-alkylation. Again, racemization of the alkylating agents during the reaction was observed in all cases. They pointed out[6b] that this reaction may be further complicated by the decomposition of the tetrabutylammonium salt to tris(2-octylbutyl)ammonium bromide, a potential alkylating agent. The analogous reactions in dimethyl sulfoxide solution showed no significant difference in the optical purities of the C- and O-alkylation products except in one reaction in which carbon tetrabromide was added, and for this case it was suggested[6b] that the reaction may involve an electron-transfer mechanism.



1 2 3

It appears that the process leading to the anomalous C-alkylation could involve ion pairs or ion-pair aggregates. Suama et al.,[4] for example, found that the lithium salt of ethyl acetoacetate undergoes 2-butylation with a much higher degree of retention than that for the corresponding sodium salt. Furthermore, the rate of alkylation at the ortho but not the para position of sodium phenolate, in acetone, increases relative to the total rate of alkylation with increasing concentration of the salt.[5] Since we had

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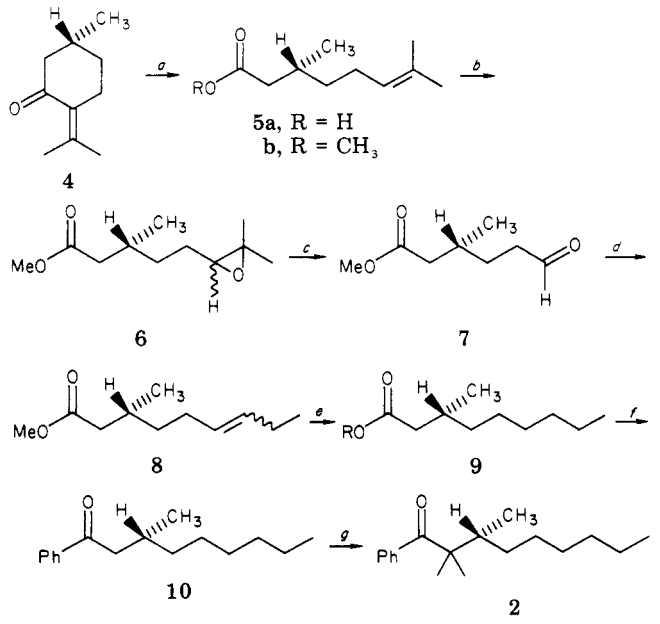
Scheme I



[a] (i) HCl, (ii) KOH, (iii) $MeOH/H_2SO_4$. [b] *m*-Perchlorobenzoic acid. [c] HIO_4. [d] $Ph_3P{=}CHCH_2CH_3$. [e] (i) H_2/Pt, (ii) H_2O/OH^-. [f] (i) LiH, (ii) PhLi. [g] KH/CH_3I.

shown that ion-pair aggregates of lithioisobutyrophenone (**1**) in weakly polar solvents are directly involved in alkylation,[7] we decided to undertake an investigation of the reaction of this simple enolate salt with optically active 2-octyl iodide in order to establish the role, if any, of aggregation in the control of stereochemistry of the substitution process. This required the determination of the absolute configuration of the C- and O-alkylation products, **2** and **3**, respectively. The configuration of **3** was readily established by acid hydrolysis to 2-octanol but that of the ketone **2** required its stereospecific synthesis.

Synthesis of (+)-1-Phenyl-2,2,3(*R*)-trimethylnonanone (2)

The starting point in our synthesis was the readily available (*R*)-(+)-pulegone (**4**), which was converted to (*R*)-(+)-citronellic acid (**5a**) by the method of Plešek.[8] This acid was in turn converted to (+)-3(*R*)-methylnonanoic acid (**9**, R = H) by standard reactions (Scheme I). It has also been obtained optically pure by Meyers and his collaborators[9] and our reported rotation is in good agreement with theirs. The absolute configuration follows from the methods of synthesis as well as from the sign of its rotation.[10]

Treatment of the lithium salt of **9** with phenyllithium afforded (−)-1-phenyl-3(*R*)-methylnonanone (**10**). The ketone was treated with 2 equiv each of potassium hydride and methyl iodide, following the method of Millard and Rathke,[11] to give the enol ether **11** (23%) and the desired ketone **2** (30%).

Alkylation of Lithioisobutyrophenone by (+)-2(*S*)-Iodooctane

Preliminary experiments using dimethoxyethane as a solvent indicated that the reaction of 2-iodooctane with lithioisobutyrophenone at room temperature was very slow and resulted in elimination to 1-*cis*-, 2-*cis*-, and 2-*trans*-octenes as well as C- and O-alkylation. At the boiling point of the solvent the reaction was complete after about 60 h, but the ratio of elimination/substitution was ~9 in comparison with ~1 at room temperature. Accordingly, the reaction with the optically active iodide was performed at 25 °C. At this temperature the reaction was better than 90% complete after 14 weeks, and an isolated yield of 38% of alkylated products (C/O = 0.56) was obtained. When dioxolane was used as the solvent at 25 °C the yield of alkylated products (C/O = 0.85) was 5.4% after 14 weeks. These reactions were accompanied by considerable racemization by lithium iodide produced during the reaction. Thus, the 2-iodooctane recovered from the reaction in dioxolane had lost 46% of its original optical activity. The optical purity of the enol ether **3** was established from the rotation of the 2-octanol obtained by acid hydrolysis. The optical purities of **2** and **3** were 3.8 ± 0.5% and 3 ± 1%, respectively, in dimethoxyethane and 78 ± 6% and 92 ± 9%, respectively, in dioxolane.

The qualitative result for both solvents is that both C- and O-alkylation proceed with net inversion of configuration. A quantitative evaluation of the degrees of stereospecificity of the two pathways is made difficult by the concurrent racemization of the 2-iodooctane, which increases in rate as the iodide concentration increases. Certainly, the extent of inversion for both C- and O- alkylation is the same within experimental error, which, however, is large. The more accurately determined value for the extent of inversion is for C-alkylation in dioxolane, and here the product was of substantially higher optical purity than that of the unreacted 2-iodooctane at the point (~10% total reaction) at which the reaction was terminated. It appears that, in these systems, if there is a mechanism that involves retention, it competes very unfavorably, or not at all, with the normal S_N2 process. Since these systems involve very tightly aggregated ion pairs, it must be concluded that ion pairing alone does not cause the C-alkylation to occur with retention.

Experimental Section

Infrared (IR) spectra were taken on a Perkin-Elmer 137 sodium chloride spectrophotometer and were calibrated with use of a polystyrene standard at 1601.8 cm^{-1}. Proton nuclear magnetic resonance (NMR) spectra were obtained at 60.00 MHz on a Varian A-60 spectrometer, using tetramethylsilane as the internal standard. Mass spectra were obtained with an MS-902 mass spectrometer, and where separations of mixtures by gas–liquid chromatography (GLC) were required prior to mass spectral analysis, a Finnigan 3200 GLC–MS system was used. Analytical GLC was performed on Perkin-Elmer 881 gas chromatograph equipped with a flame-ionization detector, using a 12 ft × $^1/_4$ in. glass column packed with 2.5% SE-30 on HMDS-treated Chromosorb G. Preparative GLC was done on a Varian Aerograph 920 instrument using a thermal conductivity detector and a 5 ft × $^1/_4$ in. metal column packed with 20% SE-30 on Gas Chrom Q. Refractive indices were measured on a Bausch and Lomb ABBE-3L refractometer. Melting points were taken on a Thomas-Hoover "Unimelt" apparatus and are uncorrected.

Optical Rotations. Rotations were measured with a Franz, Schmidt and Hänsch Co. polarimeter, using a sodium vapor lamp. Seven readings for the sample and for the empty cell were taken and the high and low values were discarded. The mean values of the remaining five readings were determined for the sample and blank, and the respective standard deviations were calculated. The mean blank rotation was subtracted from the mean sample rotation to give X, and the root mean squared value of the standard deviation (P_Y) of the mean value (Y) from three density readings was calculated. The standard deviation (P_u) in the specific rotation U is then given by $P_u = [U^2(P_x^2/X^2 + P_v^2/Y^2)]^{1/2}$ For reaction mixtures and other solutions, a 5% error in weighings

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and transfers was assumed and substituted for P_Y/Y.

Methyl 3(*R*),7-Dimethyl-6,7-epoxyoctanoate (6). To a cooled solution of (*R*)-(+)-methyl citronellate[8] (88.5 g, 0.480 mol; $n^{22.3}{}_D$ 1.4415°, $[\alpha]^{20}{}_D$ 5.69°, neat) in dichloromethane (880 mL) was added *m*-chloroperoxybenzoic acid (titrated at 86%; 96.3 g, 0.480 mol) in 1–2-g portions with stirring at 15 °C over 1 h. This produced a white suspension (*m*-chlorobenzoic acid, which is only slightly soluble in dichloromethane). The bath was removed, the reaction was stirred for 2 h, and the reaction mixture was then cooled to 5 °C. The mixture was filtered and the filtrate washed with 3% aqueous sodium hydroxide solution followed by water and dried (Na_2SO_4). The solvent was removed under reduced pressure and the resulting oil was distilled to give a mixture of diastereomeric epoxides as a colorless liquid (86.2 g, 90% distilled): bp 61.0–64.5 °C (0.05 mm); $n^{25.8}{}_D$ 1.4351°; MS *m/e* 200; IR (neat) 1743 (ester C=O) cm^{-1}; NMR (CCl_4) δ 0.95 (d, 3 H, J = 6.1 Hz, 3-methyl), 1.23 (s, 6 H, geminal methyls), 1.3–2.4 (m, 7 H, 2,3,4,5-protons), 2.4–2.7 (m, 1 H, epoxide proton), 3.62 (s, 3 H, OCH_3).

(+)-Methyl 3(*R*)-Methyl-6-oxohexanoate (7). Periodic acid (finely ground; 49.0 g, 0.215 mol) and diethyl ether (380 mL) were stirred at 10 °C, while a solution of the epoxide (43.1 g, 0.215 mol) in diethyl ether (50 mL) was added dropwise over 40 min. During addition, an amorphous white precipitate (presumably HIO_3) formed on the sides of the flask. After addition was complete the mixture was stirred for 2 h at room temperature and then cooled again to 10 °C to further decrease the HIO_3 solubility. The liquid phase was decanted and washed with aqueous phosphate buffer (pH 7), 5% aqueous sodium bicarbonate solution, and water. The organic layer was dried ($MgSO_4$), the solvent was removed under reduced pressure, and the resulting oil was distilled to give (+)-methyl 3(*R*)-methyl-6-oxohexanoate as a colorless liquid (28.5 g, 84% distilled): bp 52.5 °C (0.20 mm); $n^{27.6}{}_D$ 1.4328; $d^{24.0}{}_4$ 0.975°; MS, *m/e* 158; $[\alpha]^{24.0}{}_D$ +5.00 ± 0.06° (neat); IR (neat) 1734–1746 (two overlapping bands, aldehyde and ester C=O's), 2738 (aldehyde CH) cm^{-1}; NMR (CCl_4) δ 0.94 (d, 3 H, J = 5.8 Hz, 3-methyl), 1.1–2.6 (m, 7 H, 2,3,4,5-protons), 3.60 (s, 3 H, OCH_3), 9.69 (t, 1 H, $J \sim$ 1.5 Hz, CH=O).

The (2,4-dinitrophenyl)hydrazone derivative of the racemic ester was prepared: mp 71–72 °C (from ethanol); MS, *m/e* 338. Anal. Calcd for $C_{14}H_{18}N_4O_6$: C, 49.70; H, 5.36; N, 16.56. Found: C, 49.71; H, 5.19; N, 16.30.

(+)-3(*R*)-Methylnonanoic Acid (9, R = H). A solution of *n*-propyltriphenylphosphonium bromide (51.2 g, 0.133 mol) in dimethyl sulfoxide (150 mL) was slowly added to a solution obtained by reacting sodium hydride (6.4 g, 0.133 mol) with dimethyl sulfoxide (75 mL) at 80–85 °C. The temperature was maintained at 15 °C during the addition. (+)-Methyl 3(*R*)-methyl-6-oxohexanoate (21.0 g, 0.133 mol) in dimethyl sulfoxide was added. The mixture was stirred for 20 h at 25 °C and then poured onto ice and extracted with pentane. The dried ($MgSO_4$) pentane solution was passed through a short column of alumina (neutral, activity 1, 65 g). Removal of the solvent and distillation yielded a mixture of (*E*)- and (*Z*)-methyl 3(*R*)-methyl-6-nonenoate (8; 12 g, 49%): bp 70–71 °C (2 mm); $n^{29.4}{}_D$ 1.4360°; MS, *m/e* 184; IR (neat) 1667 (C=C), 1740 (ester C=O) cm^{-1}. The mixed ester (8.0 g, 0.130 mol) in absolute ethanol (150 mL) was catalytically hydrogenated over 10% palladium on charcoal (1.7 g). After removal of the solvent, the residue (7.1 g) was refluxed with 20% aqueous sodium hydroxide (71 mL) until a homogeneous solution was obtained (2 H). The cooled, colorless mixture was acidified with concentrated aqueous hydrochloric acid and extracted with ether. The extracts were combined and washed with water and dried ($MgSO_4$), and the solvent was removed under reduced pressure. The resulting liquid was distilled to give **9** (R = H) as a colorless oil (17.8 g, 90%): bp 105–106 °C (1.0 mm); $n^{26.1}{}_D$ 1.4334° (lit.[9] $n^{23}{}_D$ 1.4352°); $d^{24.5}{}_4$ 0.886°; MS, *m/e* 172; $[\alpha]^{24.5}{}_D$ +5.42 ± 0.03° (neat) (lit.[9] $[\alpha]^{23}{}_D$ +5.08°); IR (neat) 1710 (carboxyl C=O) cm^{-1}; NMR (CCl_4) δ 0.7–1.1 (m, 6 H, 3- and 9-methyl), 1.33–2.6 (m, 13 H, CH_2's and CH), 12.45 (s, 1 H, COOH).

(−)-1-Phenyl-3(*R*)-methylnonanone (10). Lithium hydride (0.37 g, 4.7×10^{-2} mol) and dry dimethoxyethane (20 mL) were stirred under argon, and a solution of (+)-3(*R*)-methylnonanoic acid (5.30 g, 3.1×10^{-2} mol) in dimethoxyethane was added at room temperature. The mixture was refluxed for 2 h and then cooled to 5 °C. Phenyllithium (21.7 mL of 1.7 M, 3.69×10^{-2} mol in 70:30 benzene/ether) was added dropwise over 30 min. The mixture was stirred at 25 °C for 16 h and then acidified with excess 4 M hydrochloric acid. After extraction with ether and removal of the solvent, the residue was distilled to give 2.9 g of a colorless oil, bp 112 °C (0.12 mm). This oil was shown to exist mainly of two compounds. The major component (~80% by GLC) was isolated by preparative GLC at 225 °C giving a colorless oil, identified as (−)-1-phenyl-3(*R*)-methylnonanone (2.37 g, 33%): $n^{22.3}{}_D$ 1.4998°; $d^{16.0}{}_4$ 0.945°; MS, *m/e* 232; $[\alpha]^{16}{}_D$ −6.33 ± 0.07° (neat); IR 1693 (aryl C=O) cm^{-1}; NMR (CCl_4) δ 0.8–1.1 (m, 6 H, 3- and 9-methyl), 1.29–2.81 (m, 13 H, CH_2's and CH), 7.3–7.6 (m, 3 H, meta and para H), 7.8–8.1 (m, 2 H, ortho H). Anal. Calcd for $C_{16}H_{24}O$: C, 82.36; H, 10.62. Found C, 82.70; H, 10.41.

The minor product was identified as biphenyl, mp 71 °C.

(+)-1-Phenyl-2,2,3(*R*)-trimethylnonanone (2). Potassium hydride (1.33 g of a 20% mineral oil dispersion, 6.62×10^{-3} mol) was placed in a flask, which was then flushed with argon. The mineral oil was removed with several pentane washes and dry tetrahydrofuran (15 mL) was added. (−)-1-Phenyl-3(*R*)-methylnonanone (0.77 g, 3.31×10^{-3} mol) was added dropwise with stirring at 25 °C over 5 min. Methyl iodide (0.46 mL, 7.28×10^{-3} mol, 2.2 equiv with respect to the ketone) was added dropwise by syringe over 15 min (exothermic) to produce a white precipitate. Water (5 mL) was cautiously added. Extraction with ether and removal of the solvent afforded a crude oil, which was shown (GLC at 220 °C) to consist of two major products, A and B (in the ratio 1:1.3, the latter having the longer retention time). Retention of a small portion of the mixture with aqueous hydrochloric acid in methanol diminished the GLC peak corresponding to A and resulted in the formation of a new peak at longer retention time (C). The crude mixture was separated by preparative GLC at 225 °C to yield A (0.20 g) and B (0.26 g).

Compound A was identified as (*Z*)-1-phenyl-2,3-dimethyl-1-methoxy-1-nonene (11): MS, *m/e* 260; IR (neat) 1662 (C=C), 1102 (ether CO) cm^{-1}; NMR (CCl_4) δ 0.7–1.5 (m, 17 H), 1.66 (s, 3 H, olefinic methyl shielded by phenyl), 7.29 (br s, 5 H, aromatic H's).

Compound C formed by acid hydrolysis of A is presumably a mixture of the diastereoisomeric 1-phenyl-2,3(*R*)-dimethyl-1-nonanones.

Compound B (0.26 g, 30%) was identified as (+)-1-phenyl-2,2,3(*R*)-trimethylnonanone (**2**): $n^{23.2}{}_D$ 1.4999°; $d^{16.8}{}_4$ 0.908°; MS, *m/e* 260; $[\alpha]^{16.8}{}_D$ +39.3 ± 0.2° (neat); $\alpha^{17.0}{}_D$ +4.9 ± 0.03° (14.9% w/w in ethanol); IR (neat) 1682 (aryl C=O) cm^{-1}; NMR (CCl_4) δ 0.7–1.0 (m, 6 H, 3- and 9-methyls), 1.22 (br s, 16 H, methyls and CH_2's), 2.1 (m, 1 H, 3-H), 7.2–7.5 (m, 3 H, meta and para H's), 7.6–7.9 (m, 2 H, ortho H's). Anal. Calcd for $C_{18}H_{28}O$: C, 83.02; H, 10.87. Found: C, 83.28; H, 10.88.

(*S*)-(+)-2-Iodooctane. Treatment of (−)-2(*R*)-octanol (0.176 mol), $[\alpha]^{18}{}_D$ −9.4 ± 0.1° (neat), with phosphorous triiodide in carbon disulfide by the method of Berlak and Gerrard[12] afforded (+)-2(*S*)-iodooctane (0.160 mol, 91%): bp 60.5–61.0°C (2.3 mm); $n^{21.4}{}_D$ 1.4888°; $d^{27.0}{}_4$ 1.293°; $[\alpha]^{27.0}{}_D$ +43.5 ± 0.1° (neat). The rotation corresponds to 94% optical purity on the basis of the best recorded value of $[\alpha]^{26}{}_D$ = +46.3° (neat).[13]

Reactions of (+)-2(*S*)-Iodooctane with Lithioisobutyrophenone (1). The solutions of **1** were prepared by treating a 1 M solution of *O*-(trimethylsilyl)isobutyrophenone[14] in dry diethyl ether with 1 equiv of *n*-butyllithium (1.6 M in *n*-hexane). The solvents were removed, and dry dimethoxyethane or dioxolane was added.

i. A solution of (+)-2(*S*)-iodooctane (25.0 g, 0.104 mol) and **1** (0.104 mol) in dimethoxyethane (120 mL) was stored for 14 weeks at 25 °C during which time crystalline lithium iodide separated. The reaction mixture was decomposed by water (250 mL) and the product was extracted into hexane and dried ($MgSO_4$). The solvent was removed and the residue was fractionated to give a fraction (1.06 g, 38%) containing the products **2** and **3** (**2**/**3** = 0.56 by GLC): bp 87.0–109 °C (0.06 mm); $n^{26}{}_D$ 1.4968°. This material was treated with 3 M hydrochloric acid (4 mL) in methanol (40 mL) for 1 h and, after working up as before, refractionated. The

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first fraction (2.4 g), bp 36–40 °C (0.12 mm), was a mixture of isobutyrophenone and 2-octanol from which the latter was obtained pure by chromatography over alumina (100 g, activity 1). The ketone was eluted by 1:1 hexane/diethyl ether and the alcohol by 1:9 methanol/diethyl ether. The alcohol was distilled to give pure 2-octanol (1.0 g): bp 36.0 °C (0.1 mm); $n^{22.0}_D$ 1.4261° (lit.[15] n^{20}_D 1.4264°); d^{20}_4 0.083°; $[\alpha]^{20.0}_D$ −0.3 ± 0.5° (neat); 3 ± 1% optically pure based on lit.[15] $[\alpha]^{20.4}_D$ −9.72 ± 0.05° (neat). Optically pure 2-octanol was shown to be unaffected by the above acid conditions.

The last fraction from the distillation of the hydrolysis products contained 90–95% of **2** (shown by GLC at 225 °C), bp 105.5–106.5 °C (0.06 mm). This material was redistilled to give the pure product (1.6 g): bp 112–113 °C (0.08 mm); $n^{22.9}_D$ 1.4997°; MS, *m/e* 260; $[\alpha]^{21.0}_D$ +1.5 ± 0.2° (neat); 3.8 ± 0.5% optical purity.

ii. The reaction in dioxolane was carried out on the same scale for 14 weeks and worked up in the same way. The overall yield of substitution products was 5.4% (**2**/**3** = 0.85) by GLC. Distillation afforded two fractions. From the first, bp 45–51 °C (0.3 mm), pure 2-iodooctane, n^{20}_D 1.4874°, was isolated by column chromatography over acidic alumina (activity 1) followed by GLC at 185 °C. It had $[\alpha]^{17}_D$ +26.7° (neat), corresponding to 54.5% optical purity. The second fraction (1.3 g), bp 92–118 °C (0.05 mm), consisting of **2** and **3** was separated into its constituents by preparative GLC at 225 °C. Compound **2** (0.114 g), $n^{21.5}_D$ 1.5011°, *m/e* 260, had $\alpha^{16.5}_D$ +3.8 ± 0.2° (14.9% w/w in ethanol), corresponding to 78 ± 6% optical purity. Compound **3** (0.049), $n^{20.0}_D$ 1.4982°, *m/e* 260, was made up to 1 mL with 1.2 M aqueous methanolic (1:4) hydrochloric acid and allowed to stand for 1 h by which time hydrolysis was complete (GLC). This solution had $\alpha^{18.4}_D$ −0.22 ± 0.02°. The same value was obtained for an equivalent solution of isobutyrophenone and (−)-2(*R*)-octanol, $[\alpha]^{24.0}_D$ −8.9 ± 0.1° (neat), 92% optical purity. The enol ether **3** was therefore 92 ± 9% optical pure.

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Registry No. **1**, 62416-34-6; (+)-(*R*)-**2**, 87640-37-7; (−)-(*R*)-**3**, 87640-41-3; **6** (isomer 1), 87640-32-2; **6** (isomer 2), 87640-33-3; (+)-(*R*)-**7**, 63707-85-7; (±)-**7**-DNP, 87640-34-4; (*E*)-(*R*)-**8**, 87640-35-5; (*Z*)-(*R*)-**8**, 86414-43-9; (+)-(*R*)-**9** (R = H), 52075-16-8; (−)-(*R*)-**10**, 87640-36-6; (*Z*)-(*R*)-**11**, 87640-38-8; (*R*)-(+)-methyl citronellate, 20425-48-3; *n*-propyltriphenylphosphonium bromide, 6228-47-3; 1-phenyl-2,3-dimethyl-1-nonanone (isomer 1), 87640-39-9; 1-phenyl-2,3-dimethyl-1-nonanone (isomer 2), 87640-40-2; (−)-2(*R*)-octanol, 5978-70-1; (*S*)-(+)-2-iodooctane, 1809-04-7; *O*-(trimethylsilyl)isobutyrophenone, 39158-85-5; isobutyrophenone, 611-70-1.

6,2-Methyl Migration in the Norbornane System

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A synthesis of 2-(6-*exo*-methyl-2-norbornylidene)ethanoic acid (**5**) is described; 2-(2-norbornylidene)ethanoic acid (**3**) and **5** are each treated with trifluoroacetic acid and thereby are rearranged to the respective isomeric lactones of 6-*exo*-hydroxynorbornaneethanoic acid (**4**) and 6-*exo*-hydroxy-6-*endo*-methylnorbornaneethanoic acid (**6**). Both lactones proved to be all but wholly racemic though **3** and **5** were each optically active. Thus it is demonstrated that one may have a 6,2-*endo*-methyl shift analogous to the well-known 6,2-hydride shift in the norbornane system.

In the course of structural and configurational studies in the norbornane system[6] it was discovered that a strongly acidic isomerization of optically active 2-(3,3-dimethyl-2-norbornylidene)ethanoic acid ((−)-**1**) into 7,7-dimethyl-2-*exo*-hydroxynorbornane-1-ethanoic acid (**2**) afforded all but completely racemic product. Extensive investigation led to the conclusion that the only way in which the isomerization–racemization could occur is via the well established 6,2-hydride shift in which the migrating hydride is the endo hydrogen on carbon-6 (R^2). (Scheme I, compound **2**).

Some years later the study of this isomerization–racemization was reopened,[1] the compounds in this instance being rather simpler, lacking the dependent methyl groups of **1** and **2**, i.e., compounds (−)-**3** and (+)-**4**, Scheme I. The behavior of (−)-**3** on treatment with trifluoroacetic acid led to the expected lactone which proved to be all but completely racemic through **3** had been optically active. Thus analogous isomerization–racemization occurred as with (−)-**1** → (±)-**2**.

At this juncture it occurred to the senior author that the foregoing system might be ideal for demonstrating whether or not an alkyl group might experience a 6,2-shift analogous to the 6,2-hydride shift. The only previous instance of a 6,2-alkyl shift in the norbornane system is implicit in Schleyer and Donaldson's first proposed mechanism of adamantane synthesis.[7] But subsequent work[8] no longer had recourse to the 6,2-shift. Thus the problem remained open to investigation. The compound required for study

(1) B. A. Gross, M.S. Dissertation, The University of Connecticut, 1971.

(2) Stephen E. Burkle, Postdoctoral Research Associate, The University of Connecticut, 1973.

(3) Marjorie A. Langell, B.S. Honors Thesis, The University of Connecticut, 1974.

(4) Ronald Caple, vising Professor from The University of Minnesota, Duluth, 1974. The senior author wishes to thank Professor Caple for his contribution to the synthesis of 6-*exo*-methyl-2-norbornanone.

(5) David B. Oakes, B.S. Honors Thesis, The University of Connecticut, 1982, and subsequent research leading to the completion of the problem. He was generously supported by Summer Research Fellowships from The University of Connecticut Foundation in 1981 and 1982.

(6) W. R. Vaughan, J. Wolinsky, R. R. Dueltgen, S. Grey, and F. S. Seichter, *J. Org. Chem.* **35**, 400 (1970).

(7) P. R. Schleyer and M. Donaldson, *J. Am. Chem. Soc.*, **82**, 4645 (1960).

(8) E. M. Engler, M. Farcasin, A. Levin, J. M. Cense, and P. R. Schleyer, *J. Am. Chem. Soc.*, **95**, 5769 (1973).

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