Pentacyclic Triterpene Synthesis. Synthesis and Reactions of *cis*- and *trans*-7,7,10-Trimethyl-$\Delta^{3,4}$-octalin-2-one—Preparation of DE Synthon[1a]

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Synthesis of the *cis*- and *trans*-octalones **9a** from the corresponding cis and trans dicarboxylic acids **4** and studies on the base-catalyzed alkylation of the above octalones **9a** and their α-formyl **9d** and α-cyano **9e** derivatives are described. A novel case of predominant O-methylation of a homocyclic β-keto nitrile has been observed.

In connection with our work on the synthesis of pentacyclic triterpenoids, we explored methods for the synthesis of tetracyclic intermediates comprising the ABDE rings by coupling of two fragments corresponding to the AB and DE units. To this end, we synthesized the *cis*- and *trans*-trimethyloctalones **9a** to serve as the DE unit of the projected synthetic plan. The choice of the above octalones for this scheme was dictated by the consideration that the octalones possessing a single reactive methylene group at the desired position could be alkylated directly, without taking recourse to protecting groups, to give the required tetracyclic intermediates which can be employed for the construction of the pentacyclic units.

Synthesis of the above *cis*- and *trans*-trimethyloctalones **9a** was readily achieved from the corresponding cis and trans dicarboxylic acids **4** by the steps outlined in Chart I. Catalytic reduction of the unsaturated cyanoacetate **2** gave by stereospecific reduction only the cis isomer, whereas reduction with aluminum amalgam in moist ether[2] gave a mixture of cis and trans isomers in the ratio of 1:1.

The decalindiones **7** being unsymmetrically substituted can theoretically give rise to the two isomeric enol ethers **8** and **10** and hence to the two isomeric octalones **9a** and **11** (Chart I). In the trans series, the structure of the octalone obtained by the above procedure was settled by an unambiguous synthesis of the *trans*-decalone **14** from the trans dicarboxylic acid ester **5** by two successive homologations of the acetic acid chain followed by ring closure of the resulting pimelate[4] (Chart II). This *trans*-decalone **14** was different in all respects from the *trans*-decalone **15a** obtained through the enol ether procedure. Finally, the 2 position of carbonyl group and the stereochemistry of the octalones **9a** were settled unambiguously by catalytic hydrogenation to the corresponding known *cis*- and *trans*-decalones **15a** prepared earlier by Halsall and Thomas.[3]

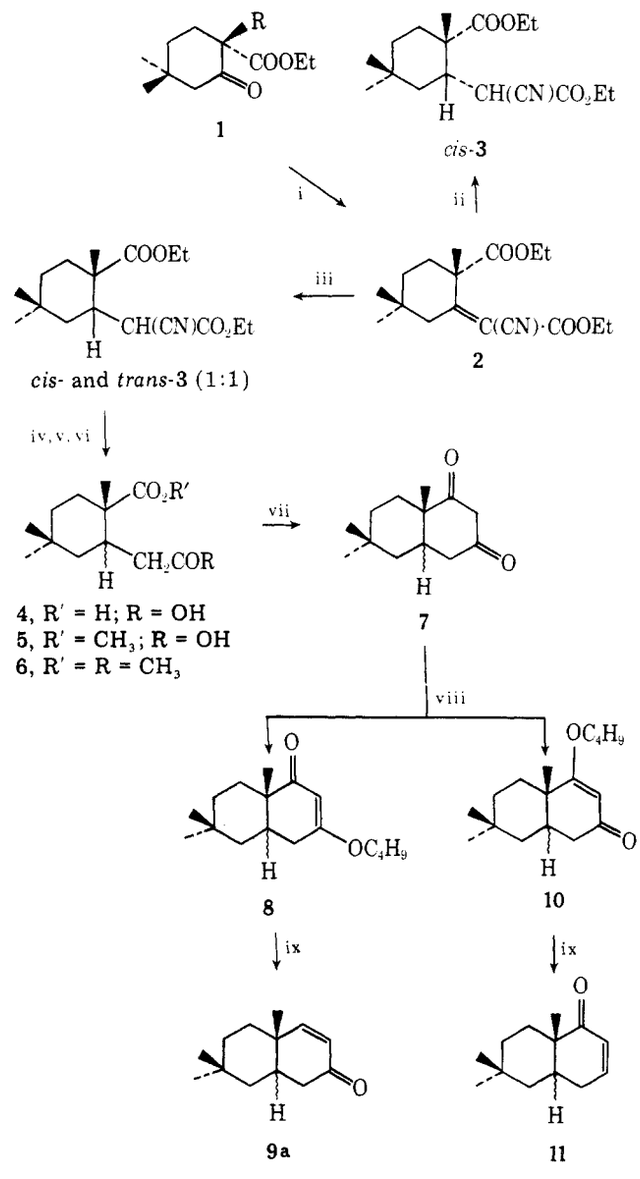
The *cis*- and *trans*-octalones **9a** possessing only one reactive center at the desired position were ideally constituted for direct base-catalyzed alkylation with appropriate alkyl halides to give the required tetracyclic intermediates. Unfortunately, attempted alkylation of either isomer in the presence of $KOBu^t$ in Bu^tOH or NaH in C_6H_6–DMF mixture with different alkyl halides was always unsuccessful.

In view of this, we examined the alkylation of the corresponding *cis*- and *trans*-β-keto aldehydes **9d** and β-keto nitriles **9e**.

Methylation of the *trans*-β-keto aldehyde **9d** gave after usual separation of O- and C-methylated products[5] the *trans*-tetramethyloctalone (*trans*-**9b**) in moderate yield. This, on catalytic hydrogenation, gave the *trans*-tetramethyldecalone (*trans*-**15b**). Attempted alkylation of the *trans*-β-keto aldehyde **9d** with ethyl bromoacetate[6] was unsuccessful. The *cis*-β-keto aldehyde **9d** however reacted under identical conditions to give exclusively the O-alkylated products.

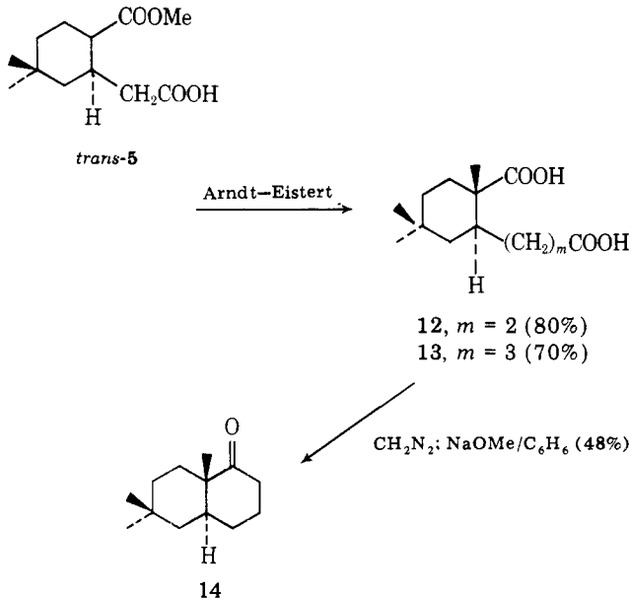
The *trans*-β-keto nitrile **9e** reacted with ethyl bromoacetate in the presence of $KOBu^t$ in Bu^tOH to give the desired C-

Chart I

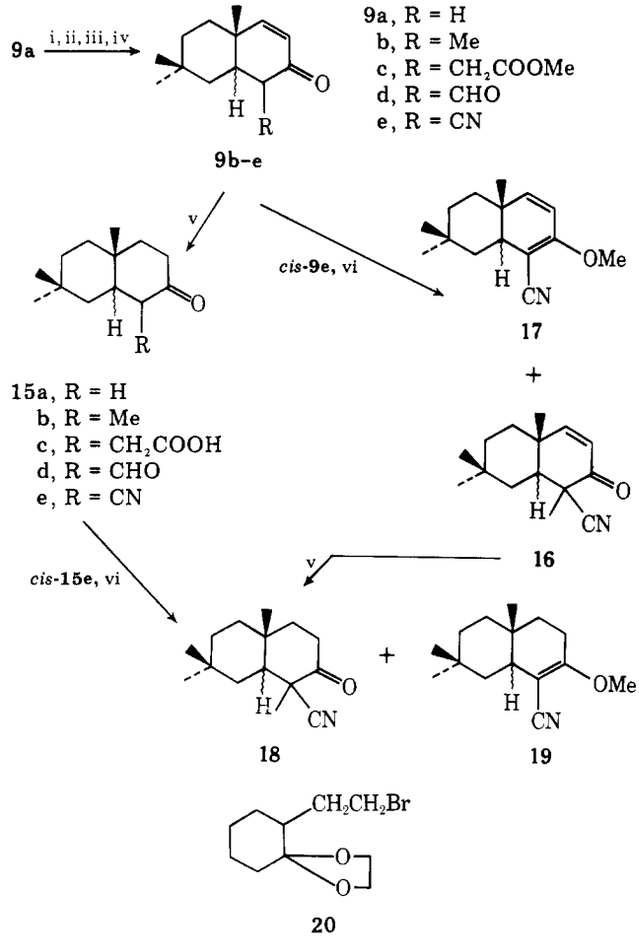


i, $CH_2(CN)CO_2Et$, AcOH, NH_4OAc, C_6H_6 (53%)
ii, 10% Pd–C (90%)
iii, Al–Hg–moist ether (86%)
iv, conc HCl and aq NaOH (90%)
v, $MeOH–H_2SO_4$ or CH_2N_2; 1 equiv of NaOH (86%)
vi, $SOCl_2$, CH_2N_2–HI, or $CdMe_2$, or $CH_2(CO_2Et)_2–H_2O$ (68%)
vii, NaOEt (94%)
viii, *i*-BuOH–H+/C_6H_6 (82%)
ix, LAH–H_2SO_4 (81%)

Chart II



alkylated product in very low yield. Much unreacted keto nitrile was recovered. Hydrolysis and esterification of the above condensation product gave the *trans*-octalone ester **9c** which on successive catalytic hydrogenation and hydrolysis afforded the *trans*-decaloneacetic acid[7] **15c**. Attempted alkylation of the *trans*-octalonenitrile **9e** with the ethylene ketal of 2-(2-oxocyclohexyl)ethyl bromide (**20**) was however less promising.



i, HCO_2Et, NaOEt (85%)
ii, MeI, K_2CO_3, Me_2CO (26%)
iii, NH_2OH·HCl, AcOH, NaOMe (80%)
iv, $BrCH_2CO_2Et$, $KOBu^t$, ^tBuOH; HCl; CH_2N_2 (10%)
v, H_2–10%-Pd-C (98%)
vi, $KOBu^t$-MeI (30–40%)

The *cis*-octalonenitrile **9e** under identical conditions however reacted with ethyl bromoacetate as well as with the bromide **20** to give in quantitative yield the corresponding O-alkylated products. No evidence of any C alkylation could be obtained in either case.

Base-catalyzed alkylation of β-keto esters and β-keto nitriles have been known to give essentially the corresponding C-alkylated products except with highly reactive alkyl halides which are known to promote O alkylation.[8] The observed exclusive O alkylation of the *cis*-β-keto nitrile **9e** with ethyl bromoacetate provided an exception to the general behavior of such β-keto nitriles[9] and encouraged us to investigate the methylation of the β-keto nitriles *cis*- and *trans*-**9e**.

Methylation of the *cis*-octalonenitrile **9e** with methyl iodide in the presence of $KOBu^t$ in Bu^tOH gave a mixture of O- and C-methylated products **16** and **17** from which the C-methylated product *cis*-**16** was obtained in ca. 30% yield. Catalytic hydrogenation of the *cis*-octalonenitrile **16** gave the corresponding decalone **18**. The predominant O methylation observed in this system thus provided an exception to the general behavior[10] of homocyclic β-keto nitriles so far reported.[11]

The *cis*-decalonenitrile **15e** was methylated under identical conditions to yield again a mixture of O- and C-methylated products, from which the C-methylated product *cis*-**18** was isolated in ca. 40% yield. It was interesting and significant to note that the methylation of *cis*-octalone **9e** and *cis*-decalone **15e** was highly stereoselective and gave only one stereoselective product, though the sense of stereoelectivity[12] remained unknown from these studies. Alkylation of the *cis*-decalonenitrile **15e** with ethyl bromoacetate followed by vigorous hydrolysis ultimately gave the *cis*-decaloneacetic acid **15c** in an extremely poor yield. Attempted alkylation of *cis*-decalonenitrile **15e** with the bromide **20** gave the C-alkylated product in an insignificant yield.

In the cis series, O alkylation is favored in all cases due to severe steric hindrance to alkylation of C-1 from both faces of the *cis*-decalone moiety. The predominant O alkylation can presumably be due to a high equilibrium concentration of the enol form and the formation of a product in which considerable 1,3-diaxial interactions are eliminated.

Our work in this direction was abandoned following the publication of Barltrop's synthesis[13] of a pentacyclic structure along similar lines.

Experimental Section

All melting points are uncorrected. Usual workup means extraction with an organic solvent, washing the extract with water, dilute acid or dilute base where necessary, followed by water again to neutrality, drying over anhydrous Na_2SO_4, and removal of solvent under reduced pressure.

Ethyl 2,5,5-Trimethylcyclohexanone-2-carboxylate (1, R = CH_3). 3,3-Dimethylcyclohexanone[14] (93 g) was condensed with diethyl oxalate (108 g) in the presence of NaOEt (503 g) in EtOH (225 mL) to afford after usual workup the crude glyoxalate which was decarboxylated[15] with soft-glass powder (ca. 4 g) at 170–180 °C until evaluation of carbon monoxide ceased. Conventional workup and distillation gave the β-keto ester (**1**, R = H, 122 g), bp 105–110 °C (10 mm).

Methyl iodide (27 mL) was added to the sodium salt of the above β-keto ester prepared from the keto ester **1** (R = H, 56 g) and Na dust (6.45 g) in benzene (300 mL), and the mixture was refluxed until a negative $FeCl_3$ test was observed (6.5 h). Usual workup gave the methylated keto ester **1** (R = Me, 56 g), bp 110–112 °C (10 mm). The **2,4-dinitrophenylhydrazone** had mp 115 °C (lit.[16] mp 111–111.5 °C). The **semicarbazone** crystallized from EtOH had mp 150 °C.

Anal. Calcd for $C_{13}H_{23}N_3O_3$: N, 15.6. Found: N, 15.4.

Ethyl 6-Ethoxycarbonyl-3,3,6-trimethylcyclohexylidene-1-cyanoacetate (2). A mixture of the above keto ester **1** (R = CH_3;

58.3 g), ethyl cyanoacetate (49.7 g), and glacial acetic acid (18 g) in benzene (145 mL) was heated to reflux with a water separator. Ammonium acetate (23.1 g) was added in four equal portions during 15 h, and the mixture was refluxed for a further 10 h after the last addition. Usual workup and distillation afforded the desired condensation product **2** (30 g) as a pale-yellow oil, bp 150–160 °C (1 mm). The recovered keto ester was recycled to afford an additional quantity (15 g) of the condensation product **2**. Redistillation, bp 155–156 °C (1 mm), gave the analytical sample.

Anal. Calcd for $C_{17}H_{25}NO_4$: C, 66.45; H, 8.14. Found: C, 66.70; H, 8.30.

***cis*-2-Carboxy-2,5,5-trimethylcyclohexane-1-acetic Acid (*cis*-4).** The unsaturated cyano ester **2** (6.2 g) in ethanol (15 mL) was stirred in an atmosphere of hydrogen in the presence of 10% Pd-on-charcoal catalyst at atmospheric pressure until the calculated amount of hydrogen was consumed (ca. 10 h). Usual workup and distillation afforded the dihydro derivative **3** (5.5 g), bp 146–147 °C (1 mm).

The compound **3** was refluxed with a mixture of concentrated HCl (50 mL) and glacial acetic acid (10 mL) for 60 h, and the solution was then concentrated under reduced pressure. The precipitated heavy oil was taken up in ether and the ether solution extracted with aqueous $NaHCO_3$ solution. Acidification of the bicarbonate extract precipitated a crystalline solid *cis*-**4** (1.2 g), mp 170–180 °C, which after one crystallization from acetone–petroleum ether had mp 189 °C, unchanged upon further crystallization.

The neutral ether solution was evaporated, and the residue (4 g) was hydrolyzed for 10 h with 10% NaOH solution (40 mL). After removal of neutral matter by extraction with ether, acidification of the alkaline solution gave an acid (*cis*-**4**, 3.5 g), mp 175–185 °C, which after crystallization from acetone–petroleum ether had mp 189 °C and was found identical with the acid described above. An analytical specimen was prepared by crystallization from acetone–petroleum ether.

Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.17; H, 8.77. Found: C, 62.85; H, 8.60. Calcd Mol Wt for $C_{12}H_{20}O_4$: 228. Found: 230 by titration.

The cis acid **4** (12 g) was esterified with anhydrous methanol (60 mL) and concentrated H_2SO_4 (3 mL) for 20 h to afford after usual workup the dimethyl ester (7 g), bp 135–140 °C (5 mm), and a crystalline acid ester (5 g), mp 146–150 °C. The latter on esterification with diazomethane gave the dimethyl ester of *cis*-**4**.

Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.62; H, 9.37. Found: C, 65.22; H, 9.01.

***cis*- and *trans*-2-Carboxy-2,5,5-trimethylcyclohexane-1-acetic Acid (*cis*- and *trans*-4).** The unsaturated cyano ester **2** (60 g) was added to Al–Hg prepared from Al foil (40 g) covered with moist ether (500 mL) containing ethanol (2 mL), and the mixture was set aside at room temperature for 7 days with addition of water (2 mL) each day.[2] It was then poured into a mixture of ice and concentrated HCl (530 mL) with vigorous stirring. The ether layer was removed, the aqueous layer was extracted with ether, and the combined ether extracts were then processed in the usual way to give the dihydro derivatives *cis*- and *trans*-**3** (52 g), bp 145–150 °C (1 mm).

The crude mixture of *cis*- and *trans*-**3** (29 g) was hydrolyzed with a mixture of concentrated HCl (290 mL) and glacial AcOH (29 mL) for 60 h and then concentrated to a small volume under reduced pressure, and the organic matter was taken up in ether. Extraction of this ether solutions with aqueous $NaHCO_3$ solution and acidification of the bicarbonate extract precipitated the trans acid **4** (12 g), mp 165–170 °C, which after crystallization from acetone–petroleum ether had mp 177–178 °C. The melting point was depressed (155–159 °C) on admixture with the cis acid **4** (mp 189 °C).

Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.17; H, 8.77. Found: C, 63.36; H, 8.75. Calcd Mol Wt for $C_{12}H_{20}O_4$: 228. Found: 225 by titration.

The neutral ether solution was concentrated and the residue (18 g) was hydrolyzed for 10 h with 10% aqueous NaOH (180 mL). Usual workup as described before gave the cis acid **4** (10 g), mp 170–180 °C, which after crystallization had mp 189 °C.

Esterification of the trans acid **4** (7 g) with methanol (35 mL) and concentrated H_2SO_4 (2.5 mL) for 20 h gave the *trans*-dimethyl ester of **4** (7 g), bp 140–142 °C (8 mm).

Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.62; H, 9.37. Found: C, 65.35; H, 9.40.

***cis*- and *trans*-2-Methoxycarbonyl-2,5,5-trimethylcyclohexane-1-acetic Acid (*cis*- and *trans*-5).** (a) The *cis*-dimethyl ester of **4** (3.72 g) was hydrolyzed for 3 h with a solution of NaOH (0.6 g) in methanol (75 mL) and water (15 mL). Methanol was removed under reduced pressure and the residual solution extracted once with ether. Acidification of the aqueous alkaline solution precipitated an oil which was taken up in ether and processed in the usual way to afford the cis acid ester **5** (3.6 g), mp 97–100 °C, which after crystallization from acetone–petroleum ether had mp 104–105 °C.

Anal. Calcd. for $C_{13}H_{22}O_4$: C, 64.46; H, 9.09. Found: C, 64.52; H, 9.31. Calcd. Mol Wt. for $C_{13}H_{22}O_4$: 242. Found: 242 by titration.

(b) Partial hydrolysis of the *trans*-dimethyl ester of **4** (6.55 g) under identical conditions afforded the trans acid ester **5** (6.3 g), mp 84–90 °C, which after crystallization from petroleum ether had mp 94–95 °C.

Anal. Calcd for $C_{13}H_{22}O_4$; c, 64.46; H, 9.09. Found: C, 63.99; H, 9.08. Calcd Mol. Wt for $C_{13}H_{22}O_4$: 242. Found: 242 by titration.

Methyl *cis*- and *trans*-2-(2-Oxopropyl)-1,4,4-trimethylcyclohexane-1-carboxylate (*cis*- and *trans*-6). The *cis*- and *trans*-methyl ketones **6** were prepared from the cis and trans acid ester **5** by three different methods. (1) A solution of the cis acid ester **5** (3.7 g) in benzene (50 mL) containing a drop of pyridine was treated with freshly distilled thionyl chloride (3.6 g) to afford on usual treatment the corresponding acid chloride as an oil (4.0 g). This was taken up in benzene (10 mL) and was added to an ethereal solution of diazomethane (2.7 g) at 0 °C. After standing 2 h at this temperature, ether was completely removed under reduced pressure. The residual crude diazo ketone was dissolved in chloroform (50 mL) and the solution vigorously shaken (5 min) with freshly distilled hydriodic acid, specific gravity 1.7 (5 mL).[17] The chloroform solution was then washed in succession with water, aqueous sodium thiosulfate, and again with water. Removal of solvent and distillation gave the methyl ketone *cis*-**6** (2.5 g), bp 125–130 °C (4 mm).

(2) The crude diazo ketone obtained from the cis acid ester **5** (4 g) as described before was dissolved in anhydrous ether (50 mL) and cooled to 0 °C, and an excess of HCl (g) was passed. Removal of solvent gave the crude chloromethyl derivative which was dissolved in glacial AcOH (50 mL) and then powdered KI (4 g) was added to it. Zinc dust (20 g) was then added slowly with stirring to the above solution at room temperature during 6 h.[18] Water (10 mL) was added, stirring continued for 1 h more, and the mixture left at room temperature overnight. It was then filtered and the inorganic residue washed with aqueous HOAc (80%). Evaporation of the acetic acid under reduced pressure and usual workup of the organic residue gave the *cis*-methyl ketone **6**, bp 145–150 °C (15 mm).

(3) The acid chloride prepared in the usual way from the cis acid ester **5** (41 g) was added to an ice-cold suspension of sodiomalonic ester [prepared from Na dust (8 g) and diethyl malonate (50 g)] in benzene (400 mL). After stirring for 2 h at 0 °C, the reaction mixture was heated on a steam bath for 2 h, cooled, and decomposed with glacial HOAc. The benzene layer was removed and concentrated under reduced pressure. The residue was heated under reflux with a mixture of concentrated HCl (100 mL), glacial HOAc (100 mL), and water (50 mL) for 9 h.[19] After cooling, the solution was neutralized with 15% NaOH solution and extracted with ether to give after usual workup the *cis*-methyl ketone **6** (30 g), bp 125–130 °C (4 mm). It gave a positive haloform test for the methyl keto group.

2,4-Dinitrophenylhydrazone crystallized from aqueous methanol had mp 114 °C. Anal. Calcd for $C_{20}H_{28}N_4O_6$: C, 57.15; H, 6.69. Found: C, 57.39; H, 6.90. The **semicarbazone** crystallized from aqueous methanol had mp 190 °C. Anal. Calcd for $C_{15}H_{27}N_3O_3$: N, 14.14. Found: N, 14.20.

(b) The trans methyl ketone **6**, bp 125–130 °C (4 mm), was similarly prepared from the trans acid ester **5** by the above methods in comparable yields. It gave a positive haloform test for the methyl keto group.

2,4-Dinitrophenylhydrazone crystallized from aqueous methanol had mp 149 °C. Anal. Calcd for $C_{15}H_{27}N_3O_3$: N, 14.14. Found: N, 14.20.

***cis*- and *trans*-7,7,10-Trimethyldecalin-2,4-dione (*cis*- and *trans*-7).** (a) A solution of cis keto ester **6** (6 g) in ethanol (10 mL) was added to NaOEt (2.03 g) in ethanol (12 mL) and the mixture refluxed under nitrogen for 11 h. Ethanol was then completely removed under pressure, and the residue was dissolved in water and extracted once with ether. Acidification of the aqueous solution precipitated the cis diketone **7** (5.5 g), mp 160–165 °C, which after two crystallizations from acetone–petroleum ether had mp 178 °C.

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.99; H, 9.61. Found: C, 75.50; H, 9.78.

(b) The trans keto ester **6** (9.32 g) under identical treatment gave the trans diketone **7** (8.0 g), mp 160–162 °C, which after crystallization from acetone–petroleum ether had mp 166 °C.

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.99; H, 9.61. Found: C, 75.16; H, 9.61.

***cis*- and *trans*-7,7,10-Trimethyl-$\Delta^{3,4}$-octalin-2-one (*cis*- and *trans*-9a.)** (a) A mixture of the cis diketone **7** (5 g), 2-butanol (11.5 mL), benzene (60 mL), and *p*-toluenesulfonic acid (0.7 g) was refluxed with a water separator until no more water separated.[20] Usual workup

and distillation afforded the enol ether *cis*-**8** (5.2 g), bp 140–145 °C (1 mm), which solidified and after crystallization from petroleum ether had mp 62–63 °C.

Anal. Calcd for $C_{17}H_{28}O_2$: C, 77.27; H, 11.36. Found: C, 77.30; H, 11.00.

A solution of the above cis enol ether **8** (26.4 g) in ether (50 mL) was added to LAH (3.7 g) in ether (200 mL). After stirring at room temperature for 3 h, the reaction mixture was decomposed with excess of 10% aqueous H_2SO_4. Usual workup gave the *cis*-octalone **9a** (15.6 g): bp 117–118 °C (5 mm); λ_{max}^{EtOH} 232 nm, log ϵ 4.0.

The **2,4-dinitrophenylhydrazone** was crystallized from ethanol–ethyl acetate: mp 209 °C[21] (lit.[3] mp 207–209 °C); $\lambda_{max}^{CHCl_3}$ 380 nm, log ϵ 4.6. Anal. Calcd for $C_{19}H_{24}N_4O_4$: N, 15.0. Found: N, 15.4. The **semicarbazone** crystallized from ethanol, mp 228 °C (dec). Anal. Calcd for $C_{14}H_{23}N_3O$: C, 67.48; H, 9.23. Found: C, 67.38; H, 9.07.

A higher boiling fraction (5 g), bp 140–150 °C (4 mm), which solidified and had mp 62–63 °C after crystallization, was identified as unreacted enol ether *cis*-**8**.

(b) The trans diketone **7** (8 g) was similarly converted to the oily *trans*-enol ether **8** (8.3 g), bp 140–145 °C (1 mm), which upon hydride reduction and acid hydrolysis gave the *trans*-octalone **9a** (6.7 g): bp 118 °C (5 mm); λ_{max}^{EtOH} 228 nm, log ϵ 3.99.

The 2,4-dinitrophenylhydrazone crystallized from ethanol–ethyl acetate had mp 178 °C.

Anal. Calcd for $C_{19}H_{24}N_4O_4$: N, 15.0. Found: N, 15.0.

The **semicarbazone** crystallized from ethanol had mp 223 °C (dec). Anal. Calcd for $C_{14}H_{23}N_3O$: C, 67.48; H, 9.23. Found: C, 67.30; H, 9.15.

***cis*- and *trans*-7,7,10-Trimethyldecalin-2-one (*cis*- and *trans*-15a).** The *cis*-octalone **9a** (1 g) in ethanol (25 mL) was stirred in an atmosphere of hydrogen in the presence of 10% Pd-on-charcoal catalyst (0.05 g) when hydrogen uptake was complete in 20 min. Usual workup gave the *cis*-decalone **15a** as a crystalline solid which after crystallization from aqueous methanol had mp 71 °C (lit.[3] mp 67.5–68 °C).

The **2,4-dinitrophenylhydrazone** had mp 193 °C (lit.[3] mp 187–189 °C). Anal. Calcd for $C_{19}H_{26}N_4O_4$: C, 60.95; H, 6.95. Found: C, 61.08; H, 6.84.

The **semicarbazone** had mp 238 °C (dec) (lit.[3] mp 225–227 °C). Anal. Calcd for $C_{14}H_{25}N_3O$: N, 16.73. Found: N, 16.50.

(b) The *trans*-octalone **9a** was similarly hydrogenated to the oily *trans*-decalone **15a,** bp 120 °C (5 mm).

The **2,4-dinitrophenylhydrazone** had mp 202 °C (lit.[3] mp 191 °C). Anal. Calcd for $C_{19}H_{26}N_4O_4$: C, 60.95; H, 6.95. Found: C, 61.44; H, 7.26.

The **semicarbazone** had mp 225 °C (dec). Anal. Calcd for $C_{14}H_{25}N_3O$: C, 66.92; H, 9.96. Found: C, 66.70; H, 9.67.

***trans*-7,7,10-Trimethyldecalin-4-one (14).** The trans acid ester **5** (1.9 g) was converted in the usual way to its acid chloride by treatment with thionyl chloride (2.5 g) in benzene (30 mL), and the crude acid chloride was then treated with diazomethane (1 g) in ether (50 mL) to afford an oily diazo ketone (2 g) which was subjected to Wolff rearrangement[22] by heating with benzyl alcohol (10 mL) and γ-collidine (10 mL) at 170–180 °C. Usual workup and hydrolysis of the resultant crude neutral ester with excess 10% trimethylcyclohexane-1-β-propionic acid (**12,** 1.5 g) which after crystallization from acetone–petroleum ether had mp 213 °C.

Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.46; H, 9.09. Found: C, 64.42; H, 8.98. Calcd Mol. Wt. for $C_{13}H_{22}O_4$: 242. Found; 242 by titration.

The above trans acid **12** (1.4 g) was esterified with diazomethane and the dimethyl ester partially hydrolyzed to the corresponding oily acid ester. This was then subjected to a second Arndt–Eistert homologation following the above procedure to give the crystalline *trans*-2-carboxy-2,5,5-trimethylcyclohexane-1-γ-butyric acid (**13,** 0.75 g) which when crystallized from benzene–petroleum ether had mp 186 °C.

Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.63; H, 9.38. Found: C, 65.73; H, 9.51.

The above dicarboxylic acid **13** was then esterified with diazomethane, and the resultant dimethyl ester (0.7 g), bp 150 °C (5 mm), was heated in benzene (10 mL) with NaOMe (0.28 g) for 10 h under nitrogen. Hydrolysis of the resultant β-keto ester and usual workup gave the *trans*-octalone **14** (0.2 g), bp 140 °C (7 mm).

The **2,4-dinitrophenylhydrazone** had mp 183 °C. Admixture with the 2,4-dinitrophenylhydrazone of the isomeric *trans*-decalone **15a** depressed the melting point to 160–170 °C.

Anal. Calcd for $C_{19}H_{26}N_4O_4$: N, 14.90. Found: N, 14.82.

The **semicarbazone** had mp 228 °C (dec). Mixture melting point with the semicarbazone of the isomeric *trans*-decalone **15a** (mp 225 °C) was depressed to 170–175 °C.

Anal. Calcd for $C_{14}H_{25}N_3O$: C, 66.92; H, 9.96. Found: C, 66.65; H, 9.58.

***trans*-1,7,7,10-Tetramethyl-$\Delta^{3,4}$-octalin-2-one (*trans*-9b).** A solution of the *trans*-octalone **9a** (2.8 g) in benzene (50 mL) was condensed with ethyl formate (5 g) in the presence of anhydrous NaOMe (2.34 g) in the usual way[5] to afford, after the usual workup, the *trans*-hydroxymethyleneoctalone **9d** (2.8 g), as an oil which responded to $FeCl_3$ test.

A solution of the above hydroxymethyleneoctalone **9d** (2.8 g) in anhydrous acetone (25 mL) containing K_2CO_3 (25 g) and methyl iodide (4 mL) was stirred under reflux for 25 h. Conventional workup gave an oil which was hydrolyzed at room temperature overnight with a mixture of methanol (9 mL), water (1 mL), and concentrated HCl (0.5 mL), and the resulting product was then separated into neutral and acidic fractions by extraction with a 2% KOH solution. Hydrolysis of the neutral oil with 10% KOH solution for 2 h under nitrogen[5] gave after conventional workup the *trans*-tetramethyloctalone *trans*-**9b,** 0.8 g), bp 115 °C (5 mm).

The **2,4-dinitrophenylhydrazone** crystallized from ethanol–ethyl acetate had mp 220 °C. Anal. Calcd for $C_{20}H_{26}N_4O_4$: N, 14.50. Found: N, 14.20.

This *trans*-tetramethyloctalone (*trans*-**9b**) was reduced catalytically in the presence of 10% Pd-on-charcoal catalyst to furnish the *trans*-tetramethyldecalone (*trans*-**15b**).

This **2,4-dinitrophenylhydrazone** crystallized from ethanol–ethyl acetate had mp 218 °C. Anal. Calcd for $C_{20}H_{28}N_4N_4$: N, 14.43. Found: N, 14.73.

The *semicarbazone* after crystallization from ethanol had mp 225 °C (dec). Anal. Calcd for $C_{15}H_{27}N_3O$: N, 15.84. Found: N, 16.09.

Attempted alkylation of the above *trans*-hydroxymethyleneoctalone (*trans*-*9d*) with ethyl bromoacetate[6] was not successful.

Attempted methylation of the corresponding *cis*-hydroxymethyleneoctalone (*cis*-*9d*) under above conditions gave exclusively the O-methyl derivative.

***trans*-7,7,10-Trimethyldecal-2-one-1-acetic Acid (*trans*-15c).** The crude hydroxymethylene derivative of the *trans*-octalone **9d** (2.8 g) prepared by the above procedure in glacial acetic acid (180 mL) containing hydroxylamine hydrochloride (1.7 g) was heated under nitrogen for 2 h at 100 °C and then completely evaporated to dryness under reduced pressure. The residue was dissolved in $CHCl_3$, and the solution was washed in succession with 2% NaOH solution and water and concentrated to give the isoxazole derivative (2.4 g). A benzene solution (120 mL) of the isoxazole was added to a solution of NaOMe (1.41 g) in methanol (25 mL) and stirred for 45 min at room temperature.[9] The benzene solution was extracted twice with ice-cold 0.5% KOH solution, and the combined alkaline extract was acidified and the liberated oil taken up in $CHCl_3$ to give the keto nitrile *trans*-**9e** (1.8 g) as a gummy solid which was directly employed for the next step.

This keto nitrile (*trans*-**9e**) in *tert*-butyl alcohol (30 mL) was added to a solution of $KOBu^t$ (4.1 g) in *tert*-butyl alcohol (30 mL) under nitrogen followed by ethyl bromoacetate (4.5 mL), and the mixture was refluxed for 3 h under nitrogen. After removal of the solvent under reduced pressure and dilution with water, the reaction mixture was extracted with ether and the ether solution washed with 0.5% KOH solution and then with water to neutrality. Concentration of the neutral ether solution left a viscous oil (0.6 g). Acidification of the aqueous alkaline extract gave the unreacted β-keto nitrile *trans*-**9e** (1.0 g).

The condensation product (0.6 g) was hydrolyzed with concentrated HCl (6 mL) for 10 h. Usual workup gave a viscous gummy acid (0.4 g) which was esterfied (diazomethane) to give the octalone methyl ester *trans*-**9c** (bp 160–162 °C (1 mm).

The **2,4-dinitrophenylhydrazone** crystallized from methanol had mp 163 °C. Anal. Calcd for $C_{22}H_{28}N_4O_6$: N, 12.60. Found: N, 12.25.

The *trans*-octalone ester **9c** (0.3 g) in ethanol (20 mL) was reduced catalytically in the presence of 10% Pd-on-charcoal catalyst to afford the *trans*-decalone ester, bp 155–160 (1 mm).

The **2,4-dinitrophenylhydrazone** crystallized from methanol had mp 191 °C (lit.[3] mp 187–189 °C). Anal. Calcd for $C_{22}H_{30}N_4O_6$: C, 59.20; H, 6.73. Found: C, 58.91; H, 6.43.

The above decalone ester (0.2 g) was hydrolyzed with an excess of 10% methanolic KOH to afford the *trans*-decaloneacetic acid (*trans*-**15c**), which after purification through its cyclohexylamine salt, mp 160 °C, and crystallization from an ether–petroleum ether mixture had mp 96–98 °C (lit.[3] mp 92–94 °C).

***cis*-1-Cyano-7,7,10-trimethyl-$\Delta^{3,4}$-octalin-2-one (*cis*-9e).** The crude hydroxymethylene compound[23] **9d,** obtained from the *cis*-octalone **9a** (0.92 (1.92 g), ethyl formate (3.6 g), and anhydrous sodium methoxide (2.0 g) in benzene (30 mL) as described for the *trans*-oc-

talone, was heated with hydroxylamine (1.14 g) in glacial acetic acid (120 mL) for 2 h at 100 °C to yield the isoxazole (1.8 g) which in benzene (12 mL) was treated with a solution of NaOMe (1.1 g) in methanol (10 mL) at room temperature.[9] Usual workup gave *cis*-β-keto nitrile, **9e** (1.7 g), mp 120–124 °C, which upon crystallization from benzene-petroleum ether had mp 128 °C.

Anal. Calcd for $C_{14}H_{19}NO$: C, 77.41; H, 8.76. Found: C, 77.89; H, 8.90.

The **2,4-dinitrophenyl hydrazone** crystallized from ethanol–ethyl acetate, mp 206 °C.

***cis*-1-Cyano-7,7,10-trimethyldecalin-2-one (*cis*-15e).** The above *cis*-octalonenitrile **9e** (1 g) in ethanol (25 mL) was stirred in an atmosphere of hydrogen in the presence of 10% Pd-on-charcoal catalyst (0.05 g) when the calculated amount of hydrogen was taken up in 30 min. Usual workup gave the decalonenitrile, **15e**, which after crystallization from ether–petroleum ether had mp 113–114 °C.

Anal. Calcd for $C_{14}H_{21}NO$: C, 76:72; H, 9.59. Found: C, 76.77; H, 9.78.

The **2,4-dinitrophenylhydrazone** had mp 260 °C (dec).

Methylation of the *cis*-Cyanooctalone 9e: Formation of *cis*-1-Cyano-1,7,7,10-tetramethyl-$\Delta^{3,4}$-octalin-2-one (*cis*-16). The *cis*-cyanooctalone **9e** (1 g) in *tert*-butyl alcohol (10 mL) was added to a solution of $KOBu^t$ (2.2 g) in *tert*-butyl alcohol (20 mL) under nitrogen followed by methyl iodide (2 mL), and the mixture was stirred under reflux for 3 h. Alcohol was then removed under reduced pressure, and the residue was diluted with water and extracted with ether. The unreacted β-keto nitrile **9e** (0.05 g) was removed by extraction of the above ether solution with 0.5% aqueous KOH. Usual workup of the neutral ether extract gave an oil (1 g), bp 135–140 °C (2 mm). This showed λ_{max}^{EtOH} 302 nm, log ε 3.79, indicative of the presence of a homoannular diene derived from predominant O methylation to give **17.**

This oil was left at room temperature for 36 h with a mixture of methanol (7 mL), water (0.5 mL), and concenrated HCl (0.5 mL). It was then diluted with brine and extracted with ether. The ether solution was then washed with 0.5% aqueous KOH until alkaline, and this alkaline solution, upon acidification, gave the *cis*-octalonenitrile **9e** (0.6 g), mp 128 °C.

The neutral ether solution upon usual workup gave the C-methylated product **16** (0.3 g), mp 87–89 °C, which after crystallization from ether–petroleum ether had mp 103 °C.

Anal. Calcd for $C_{15}H_{21}NO$: C, 77.92; H, 9.05. Found: C, 78.27; H, 9.00.

The **2,4-dinitrophenylhydrazone** crystallized from ethanol–ethyl acetate, mp 208 °C.

Anal. Calcd for $C_{21}H_{25}N_5O_4$: N, 17.03. Found: N, 16.75.

Attempted alkylation of the *cis*-cyanooctalone **9e** with ethyl bromoacetate and with the ethylene ketal of 2-(2-oxocyclohexyl)ethyl bromide (**20**) under identical conditions gave in each case exclusively the O-alkylated products in quantitative yield.

Methylation of the *cis*-Decalonenitrile 15e: Formation of *cis*-1-cyano-1,7,7,10-tetramethyldecalin-2-one (*cis*-18). The *cis*-decalonenitrile **15e** (1 g) was reacted with methyl iodide (1.5 mL) in the presence of $KOBu^t$ (0.6 g) and *tert*-butyl alcohol (20 mL) as described above, and the reaction mixture was worked up to yield an oil (1 g), bp 160–162 °C (2 mm), which had λ_{max}^{EtOH} 235 nm, log ε 3.94, indicative of the presence of a *cis*-β-methoxycrotononitrile chromophore derived through O methylation to give **19.** This oil was treated with a mixture of methanol (8 mL), water (0.5 mL), and concentrated HCl (0.5 mL) for 36 h at room temperature and then worked up as described earlier to give the *cis*-decalonenitrile **15e,** (0.6 g), mp 113 °C, and the C-methylated product **18** (0.4 g) which after crystallization from ethanol had mp 133 °C.

Anal. Calcd for $C_{15}H_{23}NO$: C, 77.25; H, 9.87. Found: C, 77.04; H, 9.65.

The **2,4-dinitrophenylhydrazone** had mp 157 °C. Anal. Calcd for $C_{21}H_{27}N_5O_4$: N, 16.94. Found: N, 17.02. Catalytic hydrogenation of the *cis*-tetramethyloctalonenitrile (*cis*-16) gave the above tetramethyldecalonenitrile (*cis*-18), confirming identical stereochemistry at C-1 in both.

***cis*-7,7,10-Trimethyldecalin-2-one-1-acetic acid (*cis*-15c).** The *cis*-decalonenitrile **15e** (13.g) was condensed with ethyl bromoacetate (5 mL) in the presence of $KOBu^t$ (3.0 g) and *tert*-butyl alcohol (30 mL) in the manner described before to yield a neutral condensation product (2 g) which was hydrolyzed by heating on a steam bath for 1 h with a mixture of methanol (8 mL), water (1 mL), and concentrated HCl (1 mL) to give after usual workup the decalonenitrile **15e** (1.1 g) and a neutral viscous oil (0.2 g). Hydrolysis of the latter with an excess of concentrated HCl under reflux for 8 h gave a gummy acid which was taken in ether, and the ether solution was extracted with aqueous $NaHCO_3$. Acidification of the bicarbonate extract precipitated a gummy solid which gradually solidified. This, after crystallization from a ether–petroleum ether mixture, had mp 190 °C.

Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.42; H, 9.52. Found: C, 71.56; H, 9.65.

Ethylene Ketal of 2-(2-Oxocyclohexyl)ethyl Bromide (20). Ethyl cyclohexanone-2-acetate (42 g), ethylene glycol (18.5 g), and PTSA (100 mg) in benzene (200 mL) were refluxed (6 h) with a Dean–Stark apparatus until no more water separated. Usual workup gave the ketal (48 g), bp 120–122 °C (5 mm), which was reduced with $LiAlH_4$ (5.6 g) in ether (160 mL) in the usual way to give after decomposition with saturated Na_2SO_4 solution and conventional workup the ketal alcohol (36 g), mp 115–118 °C (5 mm).

Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.51; H, 9.67. Found: C, 64.80; H, 9.79.

The above ketal alcohol (10 g) was added to a solution of *p*-toluenesulfonyl chloride (12 g) in pyridine (36 mL) at 0 °C. After 24 h, it was worked up to give an oily tosyl ester (20 g) which in dry acetone (50 mL) was heated under reflux for 8 h with lithium bromide (6 g) to afford after conventional workup the required bromide **20,** bp 120–122 °C (6 mm).

Anal. Calcd for $C_{10}H_{17}O_2Br$: Br, 32.1. Found: Br, 32.5.

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Registry No.—**1** (R = H), 36168-42-0; **1** (R = Me), 63648-19-6; **1** (R = Me) semicarbazone, 63548-20-9; **2,** 63548-21-0; **3,** 63548-22-1; *cis*-**4,** 63548-23-2; *cis*-**4** dimethyl ester, 63548-24-3; *trans*-**4,** 63548-25-4; *trans*-**4** dimethyl ester, 63548-26-5; *cis*-**5,** 63548-27-6; *trans*-**5,** 63548-28-7; *cis*-**6,** 63548-29-8; *cis*-**6** DNPH, 63548-30-1; *cis*-**6** semicarbazone, 63548-31-2; *trans*-**6,** 63548-32-3; *trans*-**6** DNPH, 63548-33-4; *trans*-**6** semicarbazone, 63548-34-5; *cis*-**7,** 63548-35-6; *trans* **7,** 63548-36-7; *cis*-**8,** 63548-37-8; *trans*-**8,** 63548-38-9; *cis*-**9a,** 59270-18-7; *cis*-**9a** DNPH, 59270-19-8; *cis*-**9a** semicarbazone, 63548-39-0; *trans*-**9a,** 63548-40-3; *trans*-**9a** DNPH, 63548-41-4; *trans*-**9a** semicarbazone, 63548-42-5; *trans*-**9b,** 63548-43-6; *trans*-**9b** DNPH, 63548-44-7; *trans*-**9c,** 63548-45-8; *trans*-**9c** DNPH, 63547-91-1; *cis*-**9d,** 63640-21-1; *trans* **9d,** 63547-92-2; *cis*-**9e,** 63547-93-3; *cis*-**9e** DNPH, 63547-94-4; *trans*-**9e,** 63598-04-9; **12,** 63547-95-5; **13,** 63547-96-6; **14,** 63547-97-7; **14** DNPH, 63547-98-8; 14 semicarbazone, 63548-99-9; *cis*-**15a,** 7056-56-6; *cis*-**15a** DNPH, 63548-00-5; *cis*-**5a** semicarbazone, 63548-01-6; *trans*-**15a,** 54699-31-9; *trans*-**15a** DNPH, 63548-02-7; *trans*-**15a** semicarbazone, 63548-03-8; *trans*-**15b,** 63548-04-9; *trans*-**15b** DNPH, 63548-05-0; *trans*-**15b** semicarbazone, 63548-06-1; *cis*-**15c,** 63548-07-2; *trans*-**15c** methyl ester, 93548-08-3; *trans*-**15c** methyl ester DNPH, 63548-09-4; *cis*-**15e,** 63548-10-7; *cis*-**15e** DNPH, 63548-11-8; *cis*-**16,** 63548-12-9; *cis*-**16** DNPH, 63548-13-0; **17,** 63548-14-1; *cis*-**18,** 63548-15-2; *cis*-**18** DNPH, 63548-16-3; **19,** 63548-17-4; **20,** 63548-18-5; 3,3-dimethylcyclohexanone, 2979-19-3; diethyl oxalate, 95-92-1; ethyl cyanoacetate, 105-56-6; ethyl cyclohexanone-2-acetate, 24731-17-7; 2-(2-oxocyclohexyl)ethanol, ethylene ketal, 57133-56-9.

References and Notes

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Potassium Permanganate Oxidations of Terminal Olefins and Acetylenes to Carboxylic Acids of One Less Carbon[1]

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The potassium permanganate cleavages of terminal olefins and acetylenes to prepare carboxylic acids of one less carbon have been studied under a variety of conditions. Overoxidation is a problem if the reaction is performed in an initially neutral or basic aqueous permanganate solution under heterogeneous liquid–liquid conditions or under heterogeneous liquid–liquid conditions using organic solvents and quaternary ammonium salts as phase-transfer agents. The presence of acetic acid in the two-phase liquid–liquid aqueous permanganate oxidations using organic solvents and quaternary ammonium salts leads to good yields of carboxylic acids with small amounts of overoxidized acids. The results of experiments which attempt to elucidate the overoxidation mechanism are described.

The initial goal of the present research was an exploration of the use of the operationally simple heterogeneous liquid–liquid aqueous permanganate oxidations of the commercially available even-numbered continuous chain α-olefins to prepare high purity odd-numbered carboxylic acids of one less carbon.

$$CH_3(CH_2)_nCH{=}CH_2 \rightarrow CH_3(CH_2)_nCOOH$$

It had previously been reported that 1-decene could be oxidized to nonanoic acid (91% yield, 98% purity) in the heterogeneous two-phase water–benzene system by permanganate and the phase-transfer agent Aliquat 336.[4,5] Similarly, the conversion of 1-octene to heptanoic acid (81%) had been reported using tetrabutylammonium bromide as the phase-transfer catalyst.[6]

Oxidation of the 1-decene following the published procedure[4] (a four-times more dilute aqueous permanganate solution was used to permit effective stirring as MnO_2 fills the flask) led to an excellent yield of a crude acid mixture which consisted of nonanoic acid (90%) and octanoic acid (10%). Similarly, permanganate oxidations of 1-octene and 1-dodecene led to the desired carboxylic acids which were contaminated by hexanoic acid (8%) and decanoic acid (9%), respectively. Under these reaction conditions, the desired one-carbon cleavage products are contaminated with the overoxidation product resulting from a loss of two carbons.

It seemed reasonable to speculate that the overoxidation of the α-olefins was related in some manner to the OH^- formed as a permanganate oxidation proceeds. A study of the oxidation was then undertaken.

Numerous studies have been reported in which the products and rates of product formation from oxidations by permanganate of various substrates depend on the reaction conditions and the pH if an aqueous medium is employed.[7] Mechanistic rationalizations have been advanced to account for the products and rates found during oxidations of olefinic substrates.[7a,b,e–g]

Oxidations by permanganate, although quite effective, are usually plagued by the insolubility of the organic substrate in water. Methods for effecting reaction are rapid stirring to facilitate interfacial contact between the reactants or addition of a cosolvent such as acetic acid to the aqueous phase to enhance solubility. Along with phase-transfer agents,[4,5] crown ethers have found use in solubilizing permanganate in organic solvents.[5e,7l] Acetic anhydride has been used as a solvent in permanganate oxidations.[7h–j] Surfactants in two-phase reactions can also operate as emulsion or micellar catalysts.[8]

The stoichiometry for the cleavage of α-olefins is represented by the equation:

$$3RCH{=}CH_2 + 8MnO_4^- \rightarrow 3RCO_2^- + 3HCO_2^- + 8MnO_2 + 2OH^- + 2HOH$$

Manganese(IV) dioxide is the usual product from permanganate oxidations of most organic substrates in alkaline or mildly acidic solutions. In the equation, formate could possibly undergo further oxidation to CO_2 (to produce CO_3^{2-} in a basic medium) with a net consumption of permanganate.[7a]

The permanganate oxidation of 1-octene was studied under a variety of conditions and the results are summarized in Table I.

Let us examine some of the salient features of the data recorded in Table I. The oxidation of 1-octene proceeds in aqueous permanganate under liquid–liquid heterogeneous conditions at a rate which depends on the mode of stirring and the stirring speed (entries 1, 2, and 3). The extent of overoxidation appears to be a function of reaction time (entries 1 and 2). In the presence of acetic acid (3.3 M) the oxidation is rapid and overoxidation is suppressed (entry 4). The use of pentane or benzene in the oxidation with Aliquat 336 or benzylhexa-