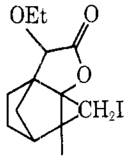

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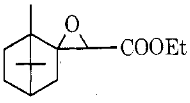

6

The formation of 2 and 4 from *dl*-camphor (1) might be rationalized by invoking Wagner–Meerwein rearrangements[11] of an intermediate of glycidic ester[12] **6.**

Experimental Section[13]

1- (2) and 4-(Carbethoxyethoxymethyl)camphene (4). To a chilled solution (0°) of 3.04 g (0.02 mol) of *dl*-camphor (1) and 4.26 g (0.03 mol) of boron trifluoride etherate in 25 ml of ether under a nitrogen atmosphere was added dropwise, over a period of 15 min, a solution of 3.42 g (0.03 mol) of ethyl diazoacetate in 5 ml of ether. The resulting solution was stirred in the dark at room temperature for 120 hr; at the end of each 24-hr period, a further 1.42 g (0.01 mol) of boron trifluoride etherate and 1.14 g (0.01 mol) of ethyl diazoacetate were added. The reaction mixture was cautiously made basic at 0° with saturated aqueous sodium bicarbonate and extracted with chloroform. The organic solution was washed with 1 *N* aqueous hydrochloric acid and water, dried ($MgSO_4$), filtered, and concentrated. Column chromatography of the oily product on silica gel with benzene elution gave 1.275 g (24% yield) of 3[8] (slower moving) and 3.36 g (63% yield) of a mixture of 2 and 4. The ir and mass spectra of the mixture were similar to those of pure 2 (see below). Its NMR spectrum (CCl_4) displayed two partly superimposed sets of signals integrated in a ratio of 2:1. The bands of the major set were found to coincide with those of 2 (see below) and the minor set contained the following diagnostic signals of 4:[14] δ_{TMS} 4.64 (s, 1 H, vinylic), 4.46 (s, 1 H, vinylic), 4.12 (q, 2 H, J = 7.2 Hz, $COOCH_2CH_3$), 4.05 (s, 1 H, OCH), 3.54 [q of d, 1 H, J = 8.5, J' = 7 Hz, $OCH(H)CH_3$], 3.35 [q of d, 1 H, J = 8.5, J' = 7 Hz, $OCH(H)CH_3$], 2.55 (br s, 1 H, allylic), 1.25 (t, 3 H, J = 7.2 Hz, $COOCH_2CH_3$), 1.16 (t, 3 H, J = 7 Hz, OCH_2CH_3), 1.05 (s, 3 H, methyl), and 0.99 (s, 3 H, methyl).

Isomerization of 4 to 2. A stirred mixture of 0.5 g (0.0019 mol) of the above mixture of 2 and 4 and 2.5 g (0.038 g-atom) of zinc dust in 20 ml of glacial acetic acid was heated at gentle reflux under an atmosphere of nitrogen for 24 hr. After cooling to room temperature, the reaction mixture was filtered and the filtrate was concentrated. Bulb-to-bulb distillation of the residue at 75° (oven temperature) (1.5 mm) gave 0.482 g (96% yield) of **2:** ir (film) 1740 (C=O) and 1650 cm^{-1} (C=C); NMR (CCl_4) δ_{TMS} 4.79 (s, 1 H, vinylic), 4.55 (s, 1 H, vinylic), 4.12 (t, 2 H, J = 7.2 Hz, $COOCH_2CH_3$), 4.01 (s, 1 H, OCH), 3.54 [q of d, 1 H, J = 8.5, J' = 7 Hz, $OCH(H)CH_3$], 3.35 [q of d, 1 H, J = 8.5, J' = 7 Hz, $OCH(H)CH_3$], 1.25 (t, 3 H, J = 7.2 Hz, $COOCH_2CH_3$), 1.20 (t, 3 H, J = 7 Hz, OCH_2CH_3), 1.05 (s, 3 H, methyl), and 0.99 (s, 3 H, methyl); mass spectrum *m/e* 266.1888 (M^+, calcd for $C_{16}H_{26}O_3$, 266.1882) and 193 (base peak).

Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.18, 72.42; H, 10.06, 9.88.

Under other applied conditions (boiling acetic acid; *p*-toluenesulfonic acid in benzene at room temperature or at reflux), the isomerization was found to proceed less effectively.

2-Ethoxy-5-(iodomethyl)-6,6-dimethyl-4-oxatricyclo[5.2.1.$0^{1,5}$]decan-3-one (5). A solution of 0.42 g (0.0016 mol) of 2 and 10 ml of 4 *N* aqueous sodium hydroxide in 10 ml of methanol was refluxed with stirring under a nitrogen atmosphere for 16 hr. After cooling to room temperature, the reaction mixture was diluted with 20 ml of water and washed twice with ether. The aqueous solution was then acidified with 1 *N* aqueous hydrochloric acid and extracted with chloroform. Work-up of the chloroform solution in the usual manner afforded 0.36 g of acidic product which, without purification, was dissolved in 20 ml of 0.5 *N* aqueous sodium bicarbonate. To this solution, 1.59 g (0.0096 mol) of potassium iodide and 0.81 g (0.0064 mol) of iodine were added.[15] After stirring at room temperature in the dark for 20 hr, the mixture was poured into a slurry of 40 ml of 1 *N* aqueous sodium hydroxide and ice. Extraction with methylene chloride followed by the usual work-up of the organic solution gave 0.471 g (82% yield based on 2) of **5:** mp 137–138° (ether); ir ($CHCl_3$) 1775 cm^{-1} (C=O); NMR ($CDCl_3$) δ_{TMS} 4.57 (s, 1 H, OCH), 4.11 [q of d, 1 H, J = 9, J' = 7 Hz, $OCH(H)CH_3$], 3.66 [q of d, 1 H, J = 9, J' = 7 Hz, $OCH(H)CH_3$], 3.51 [d, 1 H, J = 11 Hz, CH(H)I], 3.30 [d, 1 H, J = 11 Hz, CH(H)I], 1.22 (t, 3 H, J = 7 Hz, OCH_2CH_3), 1.19 (s, 3 H, methyl), and 1.10 (s, 3 H, methyl); mass spectrum *m/e* 364.0527 (M^+, calcd for $C_{14}H_{21}O_3I^{127}$, 364.0536) and 193 (base peak).

Acknowledgments. This work was generously supported by the National Research Council of Canada and the University of Alberta.

Registry No.—**1,** 21368-68-3; **2,** 55319-46-5; **4,** 55319-47-6; **5,** 55319-48-7; ethyl diazoacetate, 623-73-4.

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(10) Separation of **2** and **4** was attempted without much success by means of column and gas chromatography and by distillation. The structural assignment of **4** follows from its rearrangement to **2** (vide infra) and from the spectral data of the mixture (see Experimental Section).
(11) J. A. Berson in "Molecular Rearrangements", P. de Mayo, Ed., Interscience, New York, N.Y., 1963, Chapter 3.
(12) The reported isolation of ethyl β,β-dimethylglycidate in large quantity from the boron trifluoride catalyzed reaction of acetone and ethyl diazoacetate [W. T. Tai and E. W. Warnhoff, *Can. J. Chem.*, **42**, 1333 (1964)] serves as a precedent.
(13) The following spectrometers were used: ir, Perkin-Elmer Model 457; NMR, Varian HA-100; mass spectra, AEI MS-9. The melting point was determined on a Kofler hot stage apparatus and is uncorrected. Elemental analyses were performed by the microanalytical laboratory of this department.
(14) Three signlets at δ 4.64, 4.46, and 2.55 were most significant in assigning its structure; the corresponding hydrogen atoms of camphene appeared in the NMR spectrum taken under the same conditions at δ 4.68 (s), 4.47 (s), and 2.65 (br s).
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Activated Metals. IX. A New Reformatsky Reagent Involving Activated Indium for the Preparation of β-Hydroxy Esters[1]

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Until recently, synthesis using the direct reaction of indium metal was at best limited. Use was restricted to the preparation of triaryl- and trialkylindium compounds from the reaction of indium metal and diorganomercury compounds[3-5] and the preparation of alkylindium halides[6] from alkyl halides. We have recently reported a new procedure for the preparation of activated metals[1,7] and we have shown that by using this procedure highly reactive indium metal powders are generated.[8,9] In this paper, we would like to report that this highly reactive indium metal reacts readily with α-halo esters to give a Reformatsky-type reagent which will add to ketones and aldehydes to give β-hydroxy esters. The Reformatsky reaction using zinc metal has been used in the preparation of β-hydroxy esters for many years. Recent improvements have made this reaction a fairly reliable reaction.[7,10,11]

The activated indium powder was prepared by reducing anhydrous $InCl_3$ (Alfa ultrapure) with freshly cut potassium metal in dry, freshly distilled xylene. The mixture is

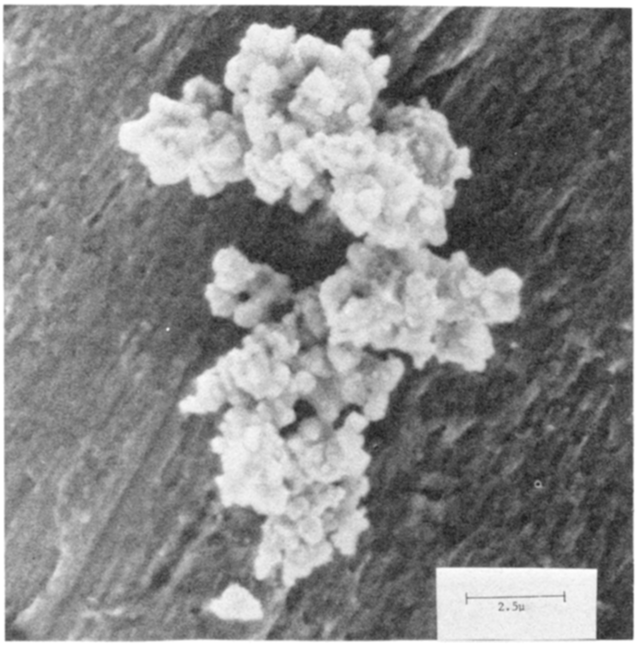


Figure 1. Activated indium prepared by reduction of $InCl_3$ with potassium in xylene.

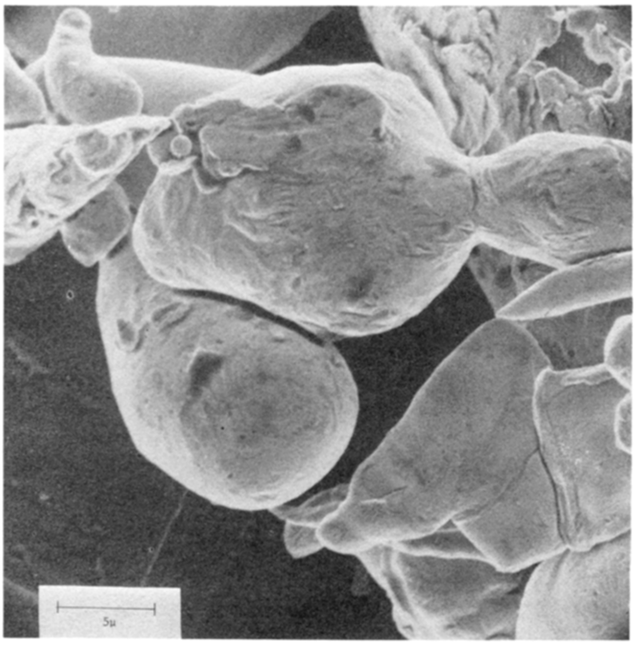


Figure 2. Commercial atomized 325-mesh indium metal.

Table I
Solvent Effect on the Yield of the Reactions with Activated Indium[a]

Carbonyl compd	Solvent	Reaction temp, °C	Reaction time, hr	% yield[b]
Cyclohexanone	Xylene	55	2	100
Cyclohexanone	Et_2O	34	12	100
Cyclohexanone	THF	66	4.5	39–71[c]
Benzaldehyde	Xylene	55	2	83–100
Benzaldehyde	Et_2O	34	6	81
Benzaldehyde	THF	66	4	67

[a] All reactions were carried out in the ratio of $In^*:BrCH_2CO_2Et:>\!\!=\!O$ = 1.0:0.95:0.95. [b] Yield was measured by GC based on $BrCH_2CO_2Et/2$ = 100% yield.[d] [c] Unreacted cyclohexanone was not completely recovered. [d] The factor of ½ is necessary because only one $-CH_2CO_2Et$ group of $BrIn(CH_2CO_2Et)_2$ adds to a ketone or aldehyde.

Table II
Effect of Stoichiometric Ratio of Ethyl Bromoacetate to Carbonyl Compounds on the Yield of the Reaction with Activated Indium[a]

Carbonyl compd	$In^*:BrCH_2CO_2Et:>\!\!=\!O$	% yield
Cyclohexanone	1.0:0.95:0.95	100
Cyclohexanone	2.1:2.0:1.0	18
Benzaldehyde	1.0:0.95:0.95	83–100
Benzaldehyde	2.1:2.0:1.0	54

[a] All reactions were carried out in xylene at 55° for 2 hr.

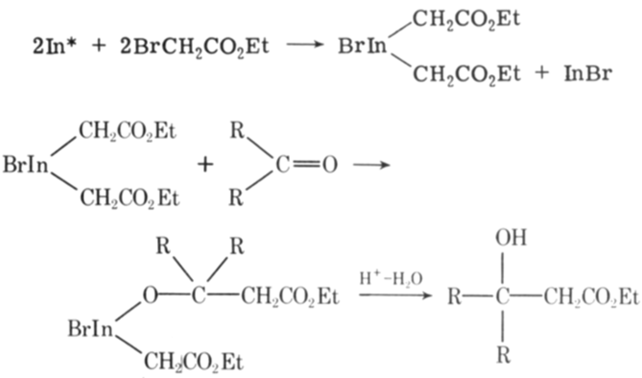
heated to reflux and stirred with a magnetic stirrer under argon for 4–6 hr, yielding a light black powder. Particle size

$$InCl_3 + 3K \longrightarrow In^* + 3KCl$$

determination on this material indicated a range of 10–0.2 μm with the average particle size being 4.0 μm. This is much smaller than that of commercially available indium powder (325 mesh). The activated indium shows a normal powder pattern of both indium metal and also the KCl. Scanning electron microscope photographs of both the activated indium (Figure 1) and commercial indium (atomized 325 mesh, Figure 2) are shown. The photographs clearly show the high surface area of the activated indium and appear to be conglomerates of even smaller crystals. Until we can get X-ray fluorescence studies done on these crystals, we cannot single out the individual crystallites of KCl or In. The material appears uniform and thus we are assuming that the conglomerates are mixtures of KCl and In crystals.

Reaction of this activated indium metal with α-halo esters is rapid. For example, reaction of a mixture of ethyl α-bromoacetate and cyclohexanone in xylene at 55° for 2 hr gives an almost quantitative yield of the corresponding β-hydroxy ester. The activated indium will also react with ethyl α-chloroacetate. In this case reaction for 7 hr at 55° in xylene gave a 42% yield of the β-hydroxy ester. In contrast, commercial indium metal (325 mesh) was treated with ethyl α-bromoacetate for periods of time up to 18 hr with a maximum yield of only 17%.

The reaction of the black indium powder with the α-bromoacetate can be readily observed by the rapid disappearance of the black powder and the formation of a brownish-yellow material. The proposed structure for the intermediate indium compounds is $(EtOCOCH_2)_2InBr$. This is based on an analysis of the material which was xylene soluble and showed an In/halide ratio of 1.05–1.00. The overall reaction scheme is shown below.



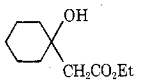
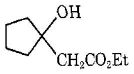
$$2In^* + 2BrCH_2CO_2Et \longrightarrow BrIn\begin{matrix}\diagup CH_2CO_2Et\\ \diagdown CH_2CO_2Et\end{matrix} + InBr$$

$$BrIn\begin{matrix}\diagup CH_2CO_2Et\\ \diagdown CH_2CO_2Et\end{matrix} + \begin{matrix}R\diagdown\\ R\diagup\end{matrix}C{=}O \longrightarrow$$

$$BrIn(CH_2CO_2Et)-O-CR_2-CH_2CO_2Et \xrightarrow{H^+-H_2O} R-\overset{OH}{\underset{R}{C}}-CH_2CO_2Et$$

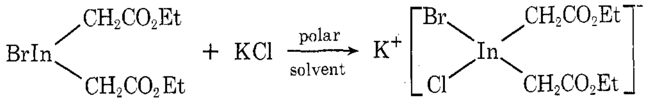
When we extracted the brownish-yellow solid with THF, in which it is much more soluble, we obtained different analysis results. In this case it was found that the K:In:ha-

Table III
Summary of Reformatsky Reaction of Carbonyl Compounds with Activated Indium and Ethyl Bromoacetate[a]

Carbonyl compd	Product	Registry no.	Solvent	Reaction temp, °C	% yield[b]
Cyclohexanone		5326-50-1	Xylene	55	100
Cyclopentanone		3197-76-0	Xylene	55	80
Benzaldehyde	$C_6H_5CH(OH)CH_2CO_2Et$	5764-85-2	Xylene	55	83-100
p-Methylacetophone	$CH_3C_6H_4C(OH)(CH_3)CH_2CO_2Et$	55319-45-4	Et_2O	34	59

[a] All reactions were carried out for 2 hr. [b] Based upon GLC analysis using internal standard, $BrCH_2CO_2Et/2 = 100\%$.[c] [c] The factor of ½ is necessary because only one $-CH_2CO_2Et$ group of $BrIn(CH_2CO_2Et)_2$ adds to a ketone or aldehyde.

lide ratio was 0.85:1.00:2.02 and it contained 25.6% of In. This fits the structure of the ate complex of $(EtOCOCH_2)_2InBr$ with KCl. Thus it appears that the composition



of this Reformatsky reagent is quite solvent dependent, with the ate complex being favored in polar solvents. We examined the effect of the solvent on the yield of the β-hydroxy ester and the results are summarized in Table I. It is readily apparent that the reactions in polar solvents gave lower yields and more side products. We attribute these results to the formation of the ate complex in polar solvents.

In order to obtain good yields of β-hydroxy esters, several reaction conditions must be carefully controlled. In the preparation of the activated indium it is very important that the molar ratio of $InCl_3$ to K be exactly 1:3. If there is an excess of either $InCl_3$ or K, side reaction products become considerable. The ratio of the carbonyl compound to the α-bromoacetate is also very critical. In order to obtain high yields, a onefold excess of the carbonyl compound is necessary; the excess carbonyl compound can be recovered later. The reason for the necessity of the excess carbonyl compound is not readily obvious. Some of the results with varying ratios of bromoacetate to ketone are summarized in Table II.

Finally, the results of reactions of a variety of carbonyl compounds with the activated indium and ethyl α-bromoacetate are summarized in Table III. In general, the yields of β-hydroxy esters are good with ketones and also with benzaldehyde in xylene and diethyl ether. However, alkyl aldehydes give relatively low yields.

Experimental Section

Materials. Cyclohexanone, cyclopentanone, benzaldehyde, *p*-methylacetophenone, ethyl bromoacetate, and ethyl chloroacetate were obtained from commercial sources. They were used without further purification. Xylene (ortho, 99%) was obtained from Aldrich and distilled over $NaAlH_4$. Diethyl ether (Fisher Anhydrous) and THF (MCB) were distilled over $LiAlH_4$ under argon. Commercial indium (325 mesh, 99.9%) and anhydrous indium trichloride were obtained from Alfa. Potassium (Baker purified) was cleaned under heptane prior to use. Activated indium metal was prepared by reducing indium trichloride with potassium in xylene by refluxing for 4–6 hr under an argon atmosphere.

Reactions Using Activated Indium. The following procedure for the conversion of cyclohexanone to ethyl (1-hydroxycyclohexyl)acetate is representative. Activated indium metal (10 mmol) was prepared from the reduction of $InCl_3$ (2.21 g, 10 mmol) and K (1.17 g, 30 g-atoms) in 25 ml of xylene in a 100-ml round-bottom flask with a side arm equipped with a septum cap under an argon atmosphere. After refluxing for 4.5 hr the mixtures were cooled down to 2° with ice–water, 1.0 g of biphenyl was added as an internal standard, and then two loaded syringes with cyclohexanone (0.93 g, 9.5 mmol) and ethyl bromoacetate (1.5 g, 9.5 mmol) were inserted into the flask via a septum cap. Both components were added simultaneously and stirred at 2° for 10 min; then the mixtures were heated to 55°. One 2-ml sample was withdrawn periodically and hydrolyzed with 2 *N* HCl solution. The organic layer was subjected to GLC. GLC analyses were carried out with an HP Model 5750 research gas chromatograph equipped with 6 ft × 0.125 in. stainless steel columns packed with 10% SE-30 on Chromosorb W. The product was identified by comparing GLC retention time with that of the authentic sample obtained from the regular zinc Reformatsky reaction.

Acknowledgment. Support of this research by the U.S. Army Research Office is gratefully acknowledged.

Registry No.—Cyclohexanone, 108-94-1; cyclopentanone, 120-92-3; benzaldehyde, 100-52-7; *p*-methylacetophenone, 122-00-9; ethyl bromoacetate, 105-36-2; ethyl chloroacetate, 105-39-5; indium, 7440-74-6; $InCl_3$, 10025-82-8; K, 7440-09-7.

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Long Range Electron Paramagnetic Resonance Coupling Interactions in Spiro Derivatives of Bicyclo[2.2.1]heptyl Semiquinone

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Nelsen,[1] Blankespoor,[2] and Russell[3] and their associates have investigated long range δ coupling constants in the semifuraquinone (1) and semidione (2) series. The observations for 1 and 2 illustrate that the interactions between