4, 60661-94-1; 5, 60661-95-2; 6, 60661-96-3; 7, 60686-99-9; 8, 38235-58-4; 9, 60661-97-4; (+)-10, 60661-98-5; (±)-10, 60687-02-7; 11, 60687-00-5; 13, 60687-01-6; 14, 55822-06-5; 16, 60661-99-6; hypochlorous acid, 7790-92-3; zinc, 7440-66-6; ethanol, 64-17-5; potassium carbonate, 584-08-7; potassium hydroxide, 1310-58-3.

References and Notes

(1) Sohio Corporation Fellow, 1975.
(2) (a) G. Wagner and A. Ginzberg, *Ber.*, **29**, 886 (1896); (b) G. Wagner and K. Slawinski, *ibid.*, **32**, 2064 (1899).
(3) G. G. Henderson and J. K. Marsh, *J. Chem. Soc.*, **119**, 1492 (1921).
(4) For a review of the chemistry of α-pinene and hypochlorous acid see J. Simonsen, "The Terpenes", Vol. II, 2d ed, Cambridge University Press, New York, N.Y., 1949, pp 172–176.
(5) Optically active pinol oxide was characterized[2b] by hydrolysis with dilute sulfuric acid to inactive pinol glycol which is now known to be *endo,endo*-6,7-dihydroxycineole.[6] Pinol chlorohydrin (**4**) is not converted by alkali to pinol glycol as indicated by Simonsen.[4]
(6) J. Wolinsky, R. O. Hutchins, and J. H. Thorstenson, *Tetrahedron*, **27**, 753 (1971).
(7) The α-pinene used by Henderson[3] was slightly dextrorotatory.
(8) The α-pinene used in this work showed $[\alpha]_D$ +46.17° and was estimated to be 95% optically pure by comparison with literature[9] values for α-pinene.
(9) F. H. Thurber and R. C. Thielke, *J. Am. Chem. Soc.*, **53**, 1030 (1931).
(10) R. L. Taylor and C. Bostock, *J. Chem. Soc.*, 444 (1912).
(11) H. Schmidt, *Chem. Ber.*, **86**, 1437 (1953).
(12) For the structure and spectra of related carvone derivatives see J. Wolinsky, J. J. Hamsher, and R. O. Hutchins, *J. Org. Chem.*, **35**, 207 (1970).
(13) M. Karplus, *J. Am. Chem. Soc.*, **85**, 2870 (1963); N. Bhacca and D. Williams, "Applications of NMR Spectroscopy to Organic Chemistry", Holden-Day, San Francisco, Calif., 1964, pp 47–51 and 136–139.
(14) D. Williams and D. A. Wilson, *J. Chem. Soc. B*, 144 (1966).
(15) R. Jones, D. Ramsey, F. Herling, and K. Dobriner, *J. Am. Chem. Soc.*, **74**, 2828 (1952).
(16) R. C. Cookson, *J. Chem. Soc.*, 282 (1954).
(17) For evidence that the formation of an epoxide from a chlorohydrin requires a trans relationship between the chlorine and hydroxyl groups see J. March, "Advanced Organic Chemistry: Reaction Mechanisms and Structure", McGraw-Hill, New York, N.Y., 1968, p 361; H. O. House, "Modern Synthetic Reactions", W. A. Benjamin, Menlo Park, Calif., 1972, p 435.
(18) It is well established that the reaction of α-pinene with electrophilic reagents in polar solvents leads to *p*-menthane derivatives.[19]
(19) D. V. Banthorpe and D. W. Whittaker, *Q. Rev., Chem. Soc.*, **20**, 380 (1966); C. M. Williams and D. Whittaker, *J. Chem. Soc. B*, 668 (1971).
(20) We have confirmed the observation that addition of hypochlorous acid to 1-methylcyclohexene[21] affords 90% of *trans*-2-chloro-1-methylcyclohexanol, 5% of *trans*-2-chloro-2-methylcyclohexanol, and 5% of *cis*-2-chloro-2-methylcyclohexanol.
(21) H. Bodot, J. Jullien, and M. Mousseron, *Bull. Soc. Chim. Fr.*, 1097 (1958).
(22) J. R. Shelton and L. H. Lee, *J. Org. Chem.*, **25**, 907 (1960).
(23) The optically inactive solid, mp 70–71 °C, described by Henderson and Marsh[3] which readily transformed into (±)-**4** is most certainly (±)-**13**.
(24) J. Wolinsky and W. Barker, *J. Am. Chem. Soc.*, **82**, 636 (1960).
(25) P. D. Bartlett and R. H. Rosenwald, *J. Am. Chem. Soc.*, **56**, 1990 (1934).

Pinol Derivatives from Lithium Aluminum Hydride Reduction of Cineole Chlorohydrin

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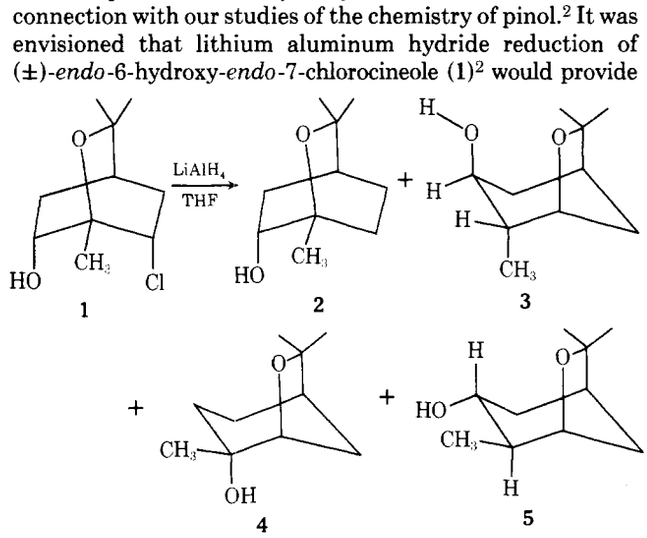
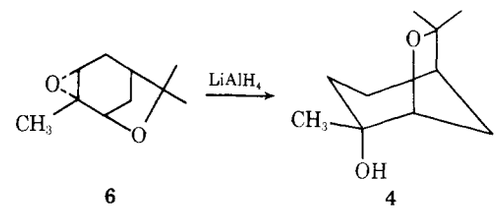
Lithium aluminum hydride reduction of (±)-*endo*-6-hydroxy-*endo*-7-chlorocineole (**1**) affords *cis*-3-hydroxy-*trans*-dihydropinol (**3**, 50%), *trans*-4-hydroxydihydropinol (**4**, 32%), *trans*-3-hydroxy-*cis*-dihydropinol (**5**, 11%), and *endo*-6-hydroxycineole (**2**, 5%). It is shown that treatment of chlorohydrin **1** with 1 equiv of hydride leads predominantly, via intermediate **14** followed by an oxygen and chlorine shift, to a pinol chlorohydrin derivative **17** which then loses chloride ion accompanied by a hydride shift to afford *trans*-dihydropinol-3-one (**12**). Ketone **12** is reduced from the least hindered side to give alcohol **3**. A competing process transforms intermediate **14** into pinol oxide (**6**) which is then reduced to alcohol **4**. Intermediate **14**, and possibly **17**, also affords small amounts of alcohol **5**.

A sample of *endo*-6-hydroxycineole (**2**) was desired in connection with our studies of the chemistry of pinol.[2] It was envisioned that lithium aluminum hydride reduction of (±)-*endo*-6-hydroxy-*endo*-7-chlorocineole (**1**)[2] would provide



a route for its preparation. However, vapor phase chromatographic analysis of the reduction product indicated the formation of a mixture comprised of four major components: *cis*-3-hydroxy-*trans*-dihydropinol (**3**, 50%), *trans*-4-hydroxydihydropinol (**4**, 32%),[3] *trans*-3-hydroxy-*cis*-dihydropinol (**5**, 11%), and *endo*-6-hydroxycineole (**2**, 5%). This publication is concerned with the evidence on which the assignment of these structures is based and the mechanism by which these compounds are formed.

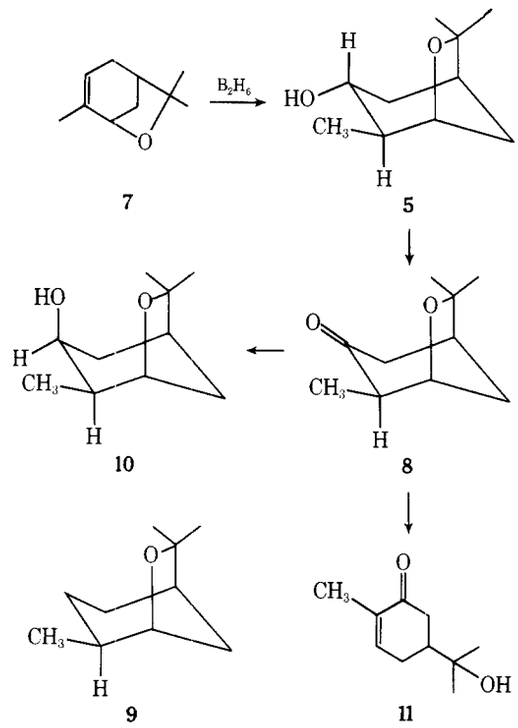
The tertiary alcohol **4** was characterized by its NMR spectrum which showed, in part, methyl singlets at δ 1.23 and 1.37 ppm and a one-proton doublet at 3.82 ppm attributed to the bridgehead hydrogen of a pinol derivative. The structure of **4** was confirmed by comparison with an authentic sample prepared by lithium aluminum hydride reduction of (±)-pinol oxide (**6**).[4]



Complete characterization of **2** was not possible because of a lack of sufficient material. However, its infrared spectrum in solution showed hydroxyl absorption at 2.78 and 2.89 μ, while its CAT improved NMR spectrum displayed methyl singlets at 1.14, 1.27, and 1.34 ppm and a one-proton quartet ($W_{1/2}$ = 20 Hz) at 3.55 ppm whose chemical shift and multi-

plicity are consistent with the assignment of an exo proton at C-6 in an oxabicyclo[2.2.2]octane ring system.

The NMR spectrum of **5** exhibited methyl singlets at 1.19 and 1.33 ppm and a methyl doublet at 1.09 ppm. A characteristic pinol bridgehead proton doublet was observed at 3.80 ppm, while a quartet at 3.62 ppm with a $W_{1/2}$ of 26 Hz indicated that the proton at C-3 was axial. This structural assignment was confirmed by an independent synthesis of **5** involving the hydroboration of (±)-pinol (**7**).

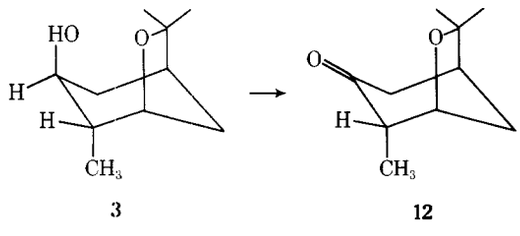


Oxidation of **5** according to the Jones procedure gave a single ketone **8**. An equatorial methyl group in **8** was indicated by the small (6 Hz) downfield NMR shift of the methyl signal when the solvent was changed from deuteriochloroform to benzene.[5] The appearance of a doublet for the C-5 bridgehead proton lends additional support for this conclusion. The dihedral angles between the axial protons at C-4 and C-8 and the quasi-equatorial proton at C-5 are approximately 90° resulting in small or negligible spin–spin coupling; consequently, a doublet results from exclusive spin coupling between the C-5 proton and the equatorial C-8 proton. *cis*-Dihydropinol (**9**) similarly shows a doublet for its C-5 bridgehead proton.

Lithium aluminum hydride reduction of ketone **8** affords alcohol **10** and only a small amount of alcohol **5** suggesting that hydride reduction occurs predominantly from the least hindered side of the molecule. The small coupling constant ($W_{1/2}$ = 13 Hz) for the C-3 proton in alcohol **10** is in accord with its equatorial assignment.

An attempt to epimerize ketone **8** with sodium methoxide in methanol failed since the ketone underwent an elimination reaction to carvone hydrate (**11**).[2,6]

Oxidation of **3** according to the Jones procedure gave ketone **12**. Axial methyl groups in **3** and **12** were indicated by a multiplet for the C-5 bridgehead proton in both compounds, and by an 18.6-Hz upfield shift of the C-4 methyl group in **12** when its NMR spectrum was determined in benzene.[5] Inspection of molecular models of these compounds indicate that the dihedral angle between the C-5 and C-4β and C-8β protons in approximately 30°; consequently, the C-5 proton should spin couple with both C-4β and C-8β protons giving rise to the observed multiplet. A small coupling constant indicated the presence of an equatorial C-3 proton in **3** which was further confirmed by a downfield shift of one of the *gem*-dimethyl groups to 1.54 ppm owing to the proximity of the axial hydroxyl group at C-3.



We now turn to a consideration of the intermediates involved in the lithium aluminum hydride reduction of **1** which results in the formation of a major product **3** where C-3 and C-5 have inverted configurations and C-4 has retained configuration. The first step in the reduction of **1** must involve the reaction of the alcohol group to afford intermediate **13.** Ionization of chloride, possibly assisted by an electrophilic aluminum species and/or neighboring oxygen, generates cation **14** (or its classical counterparts). The cation may be attacked by hydride, most likely in an intramolecular fashion,[7] to yield alcohol **5**, or by oxygen at C-6 to give pinol oxide (**6**), which is then reduced by lithium aluminum hydride to alcohol **4.** In connection with the latter conversion it is instructive to note that pinol oxide (**6**) is formed in high yield when cineole chlorohydrin (**1**) is treated with sodium hydroxide[2] or sodium hydride. Alcohol **3** forms as a consequence of a hydride shift from C-6 to give ketone **12** which is then reduced by hydride from the least hindered side of the molecule. The difficulty with accepting the proposal of the intermediacy of **14** in the formation of **3** is the requirement of a hydride ion migration which is syn to the oxygen which migrates from C-1 to C-7 of the cineole ring.

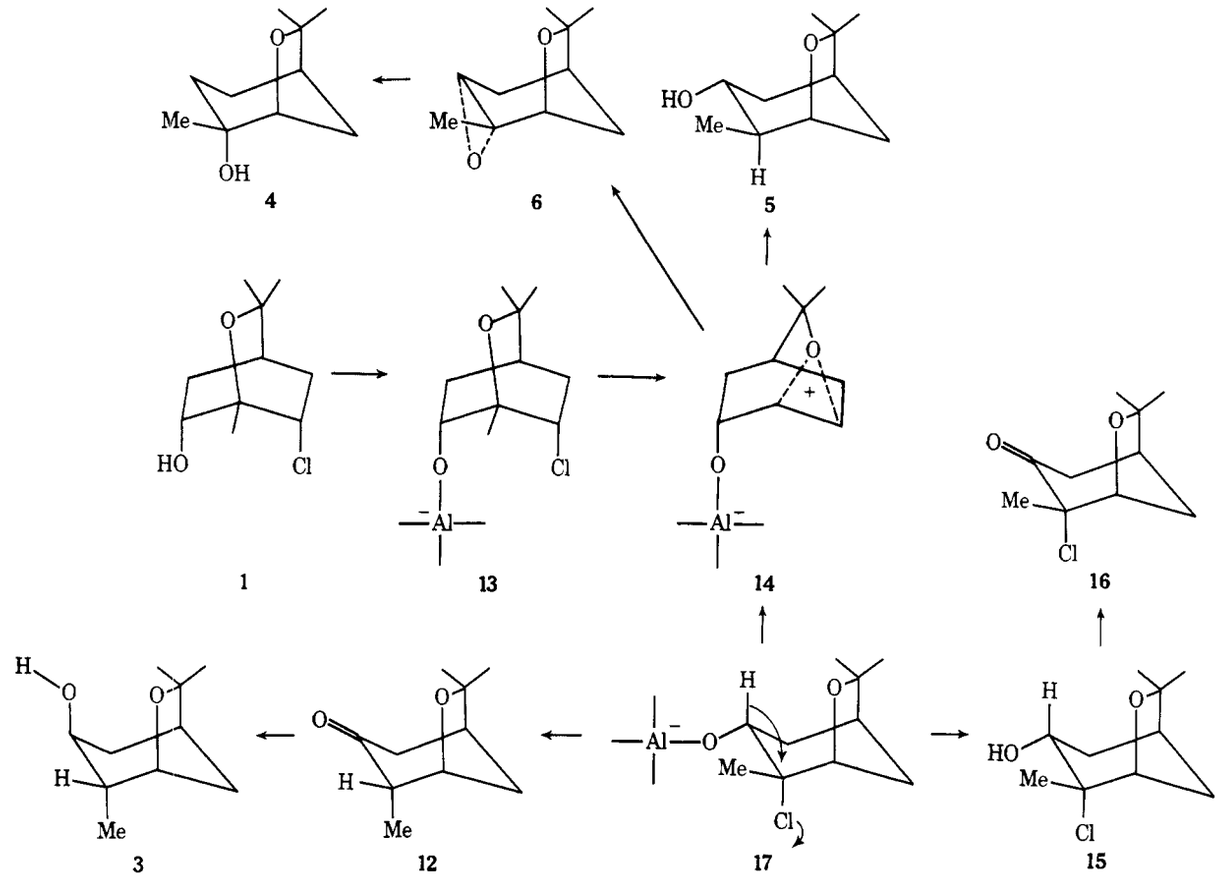
This matter was clarified when it was observed that the action of 1 equiv of hydride on chlorohydrin **1** gave little, if any, of the products obtained with excess hydride and instead yielded a mixture of starting chlorohydrin **1**, pinol chlorohydrin (**15**), and small amounts of pinol oxide (**6**) and ketone **12.**

Pinol chlorohydrin (**15**) displayed a large coupling constant for the C-3 proton indicating it to be axial. The configuration of the chlorine in **15** was established by examining the spectral properties of chloro ketone **16,** obtained by the oxidation of **15.** Chloro ketone **16** displays an NMR methyl signal at 1.63 ppm in deuteriochloroform which is shifted downfield by ca. 4 Hz in benzene. This is in accord with the presence of an equatorial methyl group at C-4. Infrared absorption at 5.81 μ and an ultraviolet maximum at 298 nm require an axial C-4 chlorine in ketone **16.**

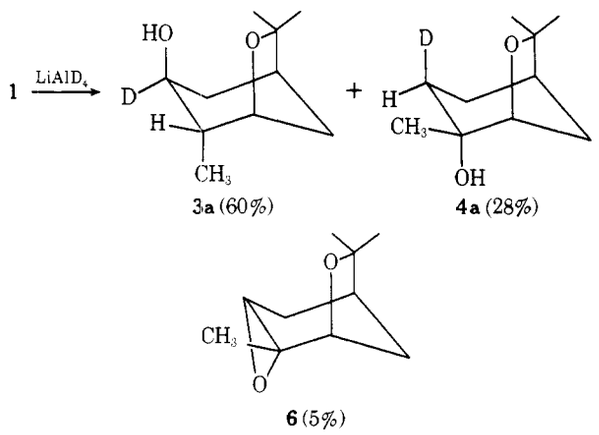
Although cineole chlorohydrin (**1**) undergoes thermal equilibration favoring pinol chlorohydrin (**15**) at temperatures above 100 °C,[8] it is stable in refluxing THF. Cineole chlorohydrin (**1**) is also recovered unchanged when treated with 1 equiv of lithium tri-*tert*-butoxyhydride in refluxing THF, suggesting that the rearrangement of **13** to **17** involves electrophilic catalysis[9] by a specific aluminum species.

It was independently established that pinol chlorohydrin (**15**), although largely recovered unchanged, is in part converted to ketone **12** by treatment with 1 equiv of lithium aluminum hydride and gives alcohol **3** when reacted with excess hydride. Intermediate **17** can now be added to the pathway involved in the conversion of **1** to **3;** in this instance the hydride at C-3 which migrates is anti to the departing chlorine at C-4.

Further verification for this path for the formation of alcohol **3** was provided by the reduction of cineole chlorohydrin (**1**) with lithium aluminum deuteride to produce the products shown in Scheme I, along with a total of 4–5% of three un-



Scheme I



identified substances, none of which appeared to be alcohol **5**.

The position of the deuterium label in alcohol **3a** was easily determined from its NMR spectrum, which showed a signal at 4.03 ppm for the C-5 bridgehead proton as the only downfield resonance. A proton at C-4 was indicated by the methyl doublet at 0.95 ppm.

Experimental Section

All boiling and melting points are uncorrected. Infrared spectra were obtained with a Perkin-Elmer Infracord. NMR spectra were recorded with a Varian Associates A-60 spectrometer. Mass spectra were measured by the Purdue University Spectral Service using a Hitachi RMU-6A spectrometer. Microanalyses were performed by Dr. C. S. Yeh and associates.

Lithium Aluminum Hydride Reduction of (±)-*endo*-6-Hydroxy-*endo*-7-chlorocineole (1). A mixture of 313 mg (1.53 mmol) of **1** and 76 mg (2.00 mmol) of lithium aluminum hydride in 25 ml of THF was heated at reflux for 56 h. The solution was cooled, water was added, and the salts were removed by filtration and washed with ether. The organic solution was dried ($MgSO_4$) and evaporated to leave 216 mg of an oil. Vpc using a 5 ft, 10% 20M Carbowax column at 110 °C furnished four products. *trans*-4-Hydroxydihydropinol (4β,7,7-trimethyl-6-oxabicyclo[3.2.1]octan-4α-ol, **4**) (retention time 29 min, 32%) showed IR (CCl_4) 2.87, 3.0, 7.26, 7.31, 8.19, 8.72, 9.18, 9.31, 9.78, and 10.92 μ; NMR ($CDCl_3$) 1.23 [s, 6, $(CH_3)_2C$–], 1.37 (s, 3, CH_3CO), 1.5–2.0 (m, 6), 2.19 (m, 2), and 3.82 ppm (d, 1, J = 5 Hz, –CHO). *endo*-6-Hydroxycineole (**2**) (retention time 36 min, 5.5%) displayed IR (CCl_4) 2.78, 2.89, 7.27, 7.32, 8.30, 8.88, 9.17, 9.41, 9.69, 10.19, and 10.98 μ; NMR ($CDCl_3$) 1.14 and 1.27 [s, 6, $(CH_3)_2C$–], 1.34 (s, 3, CH_3CO), and 3.55 ppm (q, 1, $W_{1/2}$ = 20 Hz, –CHO). *cis*-3-Hydroxy-*trans*-dihydropinol (4α,7,7-trimethyl-6-oxabicyclo[3.2.1]octan-3β-ol, **3**) (retention time 46 min, 50%) exhibited IR (CCl_4) 2.81, 2.90, 7.15, 7.27, 7.36, 9.18 and 10.05 μ; NMR ($CDCl_3$) 0.95 (d, 3, J = 8 Hz, CH_3CH–), 1.21 and 1.48 [s, 6, $(CH_3)_2CO$], 1.7–2.2 (m, 2), 2.33 (s, 1, –OH), 3.46 (m, 1, $W_{1/2}$ = 20 Hz, –CHO) and 4.06 ppm (q, 1, $W_{1/2}$ = 14 Hz, –CHOH). *trans*-3-Hydroxy-*cis*-dihydropinol (4β,7,7-trimethyl-6-oxabicyclo[3.2.1]octan-3α-ol, **5**) (retention time 55 min, 11%) showed IR (CCl_4) 2.77, 2.90, 7.26, 7.32, 8.88, 9.05, 9.53, 9.79, 10.11, 10.39, 10.58, 10.71, and 11.17 μ; NMR ($CDCl_3$) 1.09 (distorted d, 3, J = 8 Hz, CH_3CH–), 1.19 and 1.33 [s, 6, $(CH_3)_2CO$], 1.2–2.7 (m, 7), 3.62 (q, 1, $W_{1/2}$ = 26 Hz, –CHO), and 3.80 ppm (d, 1, J = 5 Hz, –CHOC).

***trans*-4-Hydroxydihydropinol (4).** A solution of 224 mg of pinol oxide (**6**) and 100 mg of lithium aluminum hydride in 10 ml of THF was heated at reflux for 8 h. The usual workup gave 226 mg of an oil which by GLC analysis was shown to be a mixture of 74% of alcohol **4** and 26% of pinol oxide (**6**). An analytical sample of **4** was obtained by GLC and showed IR and NMR spectra identical with those of alcohol **4** described above.

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.59; H, 10.59. Found: C, 70.47; H, 10.78.

Reaction of Cineole Chlorohydrin (1) with Sodium Hydride. A solution of 55 mg of **1** and 29 mg of a 57% mineral oil dispersion of sodium hydride was heated at reflux in THF for 25 h. The mixture was cooled, neutralized with dilute hydrochloric acid, and extracted with ether. The ether solution was dried ($MgSO_4$) and carefully evaporated to give 45 mg of pinol oxide (**6**) which was homogeneous according to GLC analysis on a 10% Carbowax column.

***cis*-Dihydropinol (9).** A solution of 825 mg of pinol (**7**) in 40 ml of absolute ethanol was hydrogenated at ambient temperature and

1 atm using platinum oxide as catalyst. The mixture was filtered, diluted with water, and extracted with ether. The ether solution was dried and evaporated to afford 700 mg of colorless liquid which contained 45% of **9** according to GLC analysis. A pure sample of **9** was obtained by GLC and showed IR (CCl_4) 7.27, 7.36, 7.62, 7.71, 7.95, 8.23, 8.65, 8.86, 9.08, 9.22, 9.60, 9.83, 10.05, 10.20, 10.36, 10.57, 10.71, 11.18, and 11.57 μ; NMR ($CDCl_3$) 0.89 (m, 3, CH_3CH–), 1.20 and 1.38 [s, 6, $(CH_3)_2CO$], 1.24–1.95 (m, 7), 2.38 (m, 1), and 3.98 ppm (d, 1, J = 7 Hz, –CHO–).

***trans*-3-Hydroxy-*cis*-dihydropinol (5).** To a solution of 1.49 g (9.8 mmol) of pinol (**7**) in 40 ml of dry THF at 0 °C under nitrogen was added 4.3 ml of 2.3 M borane in THF. The mixture was allowed to warm to room temperature and was stirred for 1 h. The mixture was cooled to 0 °C and 5.3 ml of 3 M sodium hydroxide solution was added followed by the dropwise (5 min) addition of 5.3 ml of 30% hydrogen peroxide. The mixture was kept at ambient temperature for 1 h, diluted with water, and extracted with ether. The ether solution was dried ($MgSO_4$) and evaporated to afford 1.6 g of liquid which was distilled to give pure **5**, bp 71–75 °C (0.18 mm), $n^{25}D$ 1.4805.

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.59; H, 10.59. Found: C, 70.66; H, 10.75.

***cis*-Dihydropinol-3-one (4β,7,7-Trimethyl-6-oxabicyclo-[3.2.1]octan-3-one, 8).** A solution of 170 mg of **5** in 10 ml of acetone was treated with Jones reagent until the orange color persisted. The usual workup gave 132 mg of ketone **8**. An analytical sample was obtained by GLC and showed IR (CCl_4) 5.83, 7.07, 7.26, 7.33, 7.44, 8.44, 8.86, 10.17, and 10.38 μ; NMR ($CDCl_3$) 1.10, 1.21, and 1.24 (s, 9, 3 CH_3C), 1.8–2.9 (m, 6), and 4.27 ppm (d, 1, J = 5.5 Hz, –CHOC).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.45; H, 9.52. Found: C, 71.62; H, 9.75.

***cis*-3-Hydroxy-*cis*-dihydropinol (4β,7,7-Trimethyl-6-oxabicyclo[3.2.1]octan-3β-ol, 10).** A solution of 300 mg (1.78 mmol) of ketone **8** in 15 ml of THF was refluxed with 55 mg (1.45 mmol) of lithium aluminum hydride for 66 h. The mixture was worked up in the usual manner to give 240 mg of an oil which on GLC analysis was shown to be 98% **10** and 2% **5**. An analytical sample of **10** was obtained by GLC and exhibited IR (CCl_4) 2.80, 6.86, 7.13, 7.27, 7.35, 8.08, 8.52, 8.89, 9.46, 9.60, 10.37, and 11.29 μ; NMR ($CDCl_3$) 1.08 (d, 3, J = 7 Hz, CH_3CH–), 1.21 and 1.54 [s, 6, $(CH_3)_2CO$], 1.6–2.8 (m, 7), 3.84 (t, 1, J = 5 Hz, –CHOH), and 4.03 ppm (d, 1, J = 7 Hz, –CHOC).

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.59; H, 10.59. Found: C, 70.81; H, 10.81.

Attempted Equilibration of Ketone 8. A 20-mg sample of ketone **8** in 0.30 ml of methanol containing sodium methoxide (from 5.2 mg of sodium) was kept at ambient temperature for 35 min. The yellow-red solution was neutralized with dilute hydrochloric acid and extracted with ether. The ether solution was dried and evaporated to yield 15 mg of a single product which was obtained pure by GLC: IR (CCl_4) 2.89 and 5.95 μ; NMR ($CDCl_3$) 1.23 [s, 6, $(CH_3)_2CO$], 1.76 (s, 3, $CH_3C{=}C$), and 6.75 ppm (m, 1, $CH{=}CCO$–). The infrared spectrum of this compound was identical with that of an authentic sample of 8-hydroxycarvotanacetone (**11**).[2,6]

***trans*-Dihydropinol-3-one (4α,7,7-Trimethyl-6-oxabicyclo[3.2.1]octan-3-one, 12).** Approximately 30 mg of alcohol **3** was treated with Jones reagent until the orange color persisted. The usual workup afforded 22 mg of an oil which was homogeneous by GLC. A sample of **12** purified by GLC showed IR (CCl_4) 5.89, 7.14, 7.31, 7.40, 8.36, 8.87, 9.04, and 10.03 μ; NMR ($CDCl_3$) 1.00 (d, 3, J = 7 Hz, CH_3CH–), 1.22 [s, 6, $(CH_3)_2CO$], 1.5–2.6 (m), and 4.20 ppm (m, 1, –CHO); NMR (C_6H_6) 0.69 (d, 3, J = 7 Hz, CH_3CH–), 1.00 and 1.10 [s, 6, $(CH_3)_2CO$], and 3.89 ppm (q, 1, $W_{1/2}$ = 14 Hz, –CHO); mass spectrum m/e (rel intensity) 168 (90), 153 (12), 125 (21), 111 (15), 110 (16), 109 (23), 99 (19), 97 (100), 82 (45), 69 (26), 67 (46), 57 (34), 55 (39), 43 (43), and 41 (39).

Cineole Chlorohydrin (1) and 1 Equiv of Lithium Aluminum Hydride. A mixture of 1.172 g (5.7 mmol) of **1** and 56 mg (1.5 mmol, 5.9 mmol of hydride) in 50 ml of THF was heated at reflux for 72 h. The usual workup gave 1.082 g of light yellow oil. Preparative TLC of 204 mg of this oil gave 100 mg of a 3:2 mixture (NMR analysis) of pinol chlorohydrin (**15**) and cineole chlorohydrin (**1**), and 22 mg of ketone **12**. An analytical sample of pinol chlorohydrin (4α-chloro-4β,7,7-trimethyl-6-oxabicylo[3.2.1]octan-3α-ol, **15**) was obtained by column chromatography on silica gel using pentane–ether as eluent followed by recrystallization from hexane: mp 77–78 °C; IR 2.90, 6.89, 7.23, 7.31, 7.70, 8.15, 8.25, 8.50, 8.92, 9.1–9.5, 9.72, 9.98, 10.42, 10.69, 11.10, 11.35, 12.00, 12.68, and 13.50 μ; NMR ($CDCl_3$) 1.18 and 1.35 [s, 6, $(CH_3)_2CO$], 1.63 (s, 3, CH_3CCl), 1.85–2.35 (m, 5), 3.98 (m, 1, –CHCl), and 4.12 ppm (d, 1, –CHO); molecular ions at m/e 184 and 186.

Anal. Calcd for $C_{10}H_{17}ClO_2$: C, 58.68; H, 8.31. Found: C, 58.39; H, 8.25.

Pinol chlorohydrin (**15**) decomposed to some extent to pinol oxide (**6**) and ketone **12** during GLC using a 15% Carbowax colum at 180 °C. The decomposition could be minimized by using a short column. GLC of the acetate derivatives of alcohols **15** and **1** could be carried out without decomposition. Thus 160 mg of the crude reaction product described above was acetylated with acetic anhydride and pyridine. The volatile reagents were removed in vacuo and the residue was separated on a 10% Carbowax column at 145 °C to give the acetate derivative of **15** (retention time 36 min): IR 5.72, 7.27, 7.31, 8.09, 9.29, and 9.52 μ; NMR ($CDCl_3$) 1.25 and 1.49 [s, 6, $(CH_3)_2CO$], 1.58 (s, 3, CH_3CCl), 2.13 (s, 3, CH_3CO_2–), 1.9–2.6 (m, 4), 4.10 (d, 1, J = 5 Hz, –CHOC), and 5.30 (m, 1, $W_{1/2}$ = 18 Hz, –CHOAc); mass spectrum m/e (rel intensity) 248 (3), 246 (8), 186 (17), 151 (96), 123 (21), 111 (36), 97 (27), and 43 (100). The acetate derivative of alcohol **1** (retention time 44 min) was identified by comparison of spectra with those of an authentic sample.[2]

Pinol Chlorohydrin (15) and Lithium Aluminum Hydride. A. 1 Equiv. A mixture of 273 mg (1.3 mmol) of **15** and 14 mg (0.37 mmol, 1.5 equiv) of lithium aluminum hydride was heated at reflux for 71 h. The mixture was worked up in the usual manner to give 240 mg of a clear oil which partially crystallized on standing. The solid was separated and recrystallized from hexane to give 72 mg of **15**, mp 74–75 °C. The mother liquor and remainder of the oil were purified by TLC and gave 57 mg of **15** and 36 mg of ketone **12**.

B. Excess Lithium Aluminum Hydride. A mixture of 500 mg (2.5 mmol) of **15** and 250 mg (6.6 mmol) of lithium aluminum hydride was heated at reflux in THF for 72 h. The usual workup gave 375 mg of clear oil. Preparative TLC of 275 mg of this oil on silica gel using pentane–acetone as eluent gave a 20:1 mixture of alcohols **3** and **5** (NMR analysis).

***trans*-4-Chlorodihydropinol-3-one (4α-Chloro-4β,7,7-trimethyl-6-oxabicyclo[3.2.1]octan-3-one 16).** To a vigorously stirred solution of 1.6 g (7.8 mmol) of **15** in 25 ml of acetone was slowly added Jones reagent (ca. 2.5 ml) until the color persisted. Isopropyl alcohol (0.25 ml) was added and the salts were removed by filtration and washed thoroughly with ether. The organic solution was washed with water, dried ($MgSO_4$), and evaporated to yield 1.4 g of colorless oil. Column chromatography using silica gel and ether–pentane gave 1 g of colorless liquid: IR 5.80, 6.83, 6.90, 7.08, 7.21, 7.30, 7.42, 7.69, 8.26, 8.42, 8.91, 9.13, 9.39, 9.58, 9.72, 9.90, 11.98, 12.15, and 12.99 μ; λ_{max} (MeOH) 298 nm (ϵ 40); NMR ($CDCl_3$) 1.15 and 1.20 [s, 6, $(CH_3)_2CO$], 1.63 (s, 3, CH_3CCl), 2.0–3.0 (m, 5), and 4.20 ppm (d, 1, –CHO); NMR (C_6H_6) 0.97 [s, 6, $(CH_3)_2CO$], 1.70 (s, 3, CH_3CCl), 1.8–2.2 (m, 5), and 4.02 ppm (d, 1, –CHO); mass spectrum m/e (rel intensity) 204 (13), 202 (39), 167 (15), 123 (18), 116 (15), 109 (22), 97 (100), 95 (10), 90 (12), 89 (11), 83 (16), 82 (10), 81 (50), 79 (17), 69 (29), 67 (11), 59 (12), 55 (25), 53 (28), 43 (72), 41 (64), and 39 (42).

Anal. Calcd for $C_{10}H_{15}ClO_2$: C, 59.26; H, 7.41; Cl, 17.53. Found: C, 59.19; H, 7.52; Cl, 17.40.

Reduction of Cineole Chlorohydrin (1) with Lithium Aluminum Deuteride. A mixture of 238 mg (1.39 mmol) of **1** and 100 mg (9.05 mmol) of lithium aluminum deuteride was heated at reflux in 20 ml of THF for 53 h. The usual workup gave 190 mg of clear oil which was separated into the following five components by GLC using a 10% Carbowax column at 110 °C (a) pinol oxide (**6**, retention time 5 min, 5%); (b) alcohol **4a** (retention time 15 min, 28%), showed a molecular ion at m/e 171; (c) hydroxycineole **2** (retention time 20 min, ca. 3%), displayed a molecular ion at m/e 171; (d) alcohol **3a** exhibited NMR signals at 0.95 (d, 3, J = 7.5 Hz, CH_3CH–), 1.21 (s, 3, CH_3CO), 1.49 (s, 3 CH_3CO), and 4.07 ppm (q, 1, $W_{1/2}$ = 23 Hz, –CHO); molecular ion at m/e 171; and (e) an alcohol tentatively assigned as *trans*-3-hydroxy-*trans*-dihydropinol (4α,7,7-trimethyl-6-oxabicyclo-[3.2.1]octan-3α-ol) (retention time 58 min, 2%) showed NMR ($CDCl_3$) 0.88 (d, 3, J = 6 Hz, CH_3CH–), 1.18 and 1.40 [s, 6, $(CH_3)_2CO$], and 4.21 ppm (m, 1, $W_{1/2}$ = 26 Hz, –CHO); molecular ion at m/e 171.

Registry No.—**1**, 60760-99-8; **2**, 60761-00-4; **3**, 60761-01-5; **3a**, 60705-66-0; **4**, 60761-02-6; **5**, 60761-03-7; **6**, 38235-59-5; **7**, 60761-04-8; **8**, 60705-67-1; **9**, 60761-05-9; **10**, 60761-06-0; **11**, 7712-46-1; **12**, 60705-68-2; **15**, 60705-69-3; **15** acetate, 60705-70-6; **16**, 60705-71-7; *trans*-3-hydroxy-*trans*-dihydropinol, 60761-07-1; $LiAlH_4$, 16853-85-3; $LiAlD_4$, 14128-54-2.

References and Notes

(1) (a) Abstracted in part from the Ph.D. Thesis of J.H.T., Purdue University, June 1970; (b) Sohio Fellow, 1975.
(2) J. Wolinsky, R. O. Hutchins, and J. H. Thorstenson, *Tetrahedron*, **27**, 753 (1971).
(3) Cis and trans refers to the configuration of the substituents at C-3 and C-4

relative to the oxide bridge.
(4) K. Pialkowski and H. Kuzynski, *Rocz. Chem.*, **35**, 239 (1961).
(5) D. H. Williams and D. A. Wilson, *J. Chem. Soc. B*, 144 (1966).
(6) H. Rupe and P. Schlochoff, *Ber.*, **38**, 1719 (1905).
(7) B. Franzus and E. I. Snyder, *J. Am. Chem. Soc.* **85**, 3902 (1963); W. T. Borden, *ibid.*, **90**, 2197 (1968).
(8) Work by Martin K. Vogel to be published.
(9) H. Kwart and T. Takeshita, *J. Org. Chem.*, **28**, 670 (1970); Y. Chretien-Bessiere, H. Desalbres, and J. Montheard, *Bull. Soc. Chim. Fr.*, 2546 (1960).

Selective Halogen–Lithium Exchange in 2,5-Dibromobenzenes and 2,5-Dibromopyridine[1]

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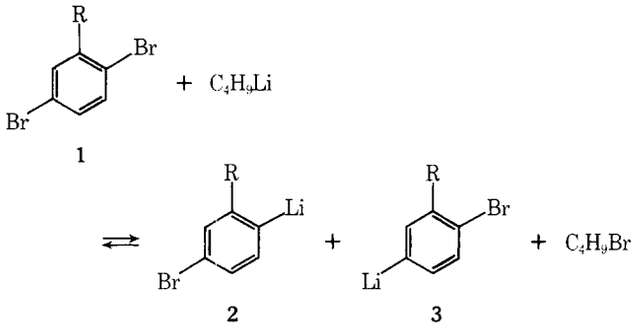
Reaction of a series of 2,5-dibromo-substituted aromatic systems with 1 equiv of *n*-butyllithium at −100 °C results in high selectivity of halogen–metal exchange when the substituent contains unshared electrons. The results suggest that product distribution at −100 °C is determined by thermodynamic rather than kinetic factors. Fair to excellent yields of derivatives of the monolithium intermediates have been obtained. Reaction of 2,5-dibromopyridine with 1 equiv of *n*-BuLi gives exclusively 2-bromo-5-lithiopyridine, which was converted in high yield into 2-bromo-5-deuteriopyridine. Reactions of 2- and 3-lithiopyridine, including their exchange with 2- and 3-bromopyridine, are described.

While selective metalation of substituted aromatic systems with alkyllithium generally occurs ortho to groups containing unshared electrons, an effect attributed to coordination of lithium with the attached functional group,[2] there has been little attention afforded[3] to selective halogen–lithium exchange in substituted dibromobenzenes (Scheme I). Extensive studies by Gilman and his co-workers[4] have established that halogen–metal exchange involves an equilibrium between reactants and products in which the lithium atom resides principally on the more electronegative carbon atom. Thus, one might anticipate that exchange in dibromobenzenes of type **1** would lead to a thermodynamically controlled mixture of **2** and **3**, possibly independent of kinetic factors which might influence the proportion of **2** and **3** formed initially.

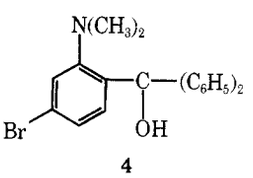
Scheme I



Since we were specifically interested in possible utilization of intermediates of type **2** and/or **3** for synthetic purposes, we have examined exchange in **1** with 1 equiv of *n*-C_4H_9Li in tetrahydrofuran (THF) at very low temperature (−100 °C). The course of reactions was determined by examining aliquots quenched with water, which were subsequently analyzed for starting material and the isomeric monobromobenzenes derived from **2** and **3** by GLC and/or NMR. With the exception of **1e**,[5] exchange was quite rapid and no appreciable change in ratio of products was observed after a few minutes. The results obtained are shown in Table I.

It is apparent that the product distribution shown in Table I does not correlate with Hammett σ functions (electrophilic substitution);[2b] however, with the possible exception of carboxylate,[7] the lithium atom in the product is preferentially located on the most electronegative carbon atom as judged by the inductive effect of the substituent. Whether this result is indeed a function of the inductive effect or a consequence of stabilization of the product by coordination of lithium with the substituent is not known; results with 2,5-dibromopyridine, discussed subsequently, suggest the latter and that the products are those determined by thermodynamic control.

In certain cases the aryllithium derivatives of **1** were elaborated by reaction with electrophiles. Warming the product derived from **1a** effected alkylation by *n*-C_4H_9Br, formed by exchange, to give a 70% yield of 5-bromo-2-*n*-butyltoluene and 2-bromo-5-*n*-butyltoluene in the approximate ratio of 3/7. Decomposition of the product from **1c** with water gave a 70% yield (isolated) of 3-bromo-*N*,*N*-dimethylaniline; reaction of the product from **1c** with benzophenone gave carbinol **4**, isolated pure in 34% yield. Treatment of the aryllithium obtained from **1d** with benzophenone gave 5-bromo-1,1-diphenylphthalide (**5**, pure 42% yield) while reaction of the product



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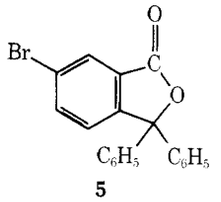

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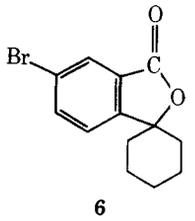

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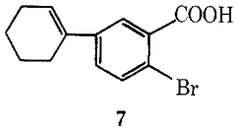

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from **1d** with cyclohexanone gave lactone **6** and the acid **7**, isolated pure in 45 and 5% yields, respectively. The structure of **7** was assigned by comparison of its NMR spectrum with those of methyl 2-bromobenzoate and methyl 3-bromobenzoate.[8]

Reaction of 2,5-dibromopyridine (**8**) with 1 equiv of *n*-C_4H_9Li at −100 °C was rapid and complete and gave >99% 2-bromo-5-lithiopyridine (**9**, Scheme II). The product obtained by addition of water was essentially pure 2-bromopyridine (**10**); 3-bromopyridine was detectible (~1%) by GLC. Elaboration of **9** with D_2SO_4 gave a quantitative yield of 2-