Addition of Butyl- and Phenyllithium to Thujones

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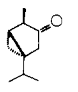
Addition of butyl- and phenyllithium to α-thujone (1) and to β-thujone (2) has been studied. The reaction produces optically active tertiary alcohols useful for the preparation of several intermediates in the synthesis of chiral compounds. The present highly strained ketones are also suitable to study the stereochemistry of addition; some torsional strain to attack by BuLi from the α-side is shown by 1 (ca. 76% α vs. 24% β), while 2 produces only the 3-butylneoisothujol as a result of addition from the α-face. A surprising exclusive attack from the β-face is exerted by PhLi; a hypothesis based on a late transition state is proposed to explain the observed anomaly.

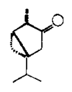
Thujone occurs in nature widely distributed; it forms the main constituent of several important volatile oils, e.g., α–thujone in oil of thuja (*Thuja occidentalis*) and sage (*Salvia officinalis* L.) and β-thujone in oil of tansy (*Tanacetum vulgare* L.) and wormwood (*Artemisia absinthium* L.), and it also occurs in a number of less important oils.[1] We have isolated thujone from the oil of *Aloysia polystachia* as the main constituent (80%) and it was therefore desirable to examine some chemical transformations of thujone as a potential chiral synthon in the synthesis of optically active compounds. With the same aim, the use of thujone has been recently reported in the synthesis of two optically pure sesquiterpenes[2] and one steroid analogue.[3]

At the same time the structural features of thujone make it a useful tool to study the stereochemistry of addition of organometallic compounds to the carbonyl group; studies of this type on cyclopentanones are scarce compared with the abundant information on cyclohexanones.[4] Since we have developed a considerable experience in the preparation of high purity organolithium compounds,[5] the study of the addition of butyl- and phenyllithium to thujone has been carried out with the double purpose of transforming thujone into a useful intermediate for the organic synthesis of chiral compounds and of making some contribution to the understanding of the several factors that govern the stereochemistry of the addition.

Results

Thujone occurs in nature in the form of two diasteroisomers, viz., (−)-α-thujone and (+)-β-thujone, more properly called (−)-thujone (1) and (+)-isothujone (2).





(−)-α-thujone (1) (+)-β-thujone (2)

Table I. Reaction of Thujone (81.5% 1 and 18.5% 2) with *n*-Butyllithium

entry	R[a]	solvent	temp,[b] °C	react time, h	yield,[c] %
1	1:2	ligroin[d]	25	1	81
2	1:2	ligroin	30	1	76
3	1:2	ligroin	45	1[e]	74
4	1:5	ligroin	25	1	87
5	1:5	ligroin	40	1[e]	81
6	1:2	ligroin-THF (1:1)	25	1	64

[a] Thujone:BuLi molar ratio. The thujone solution was added to the BuLi solution. [b] The addition was always carried out at 0 °C, and then the reaction mixture was heated to the stated temp. [c] Average of at least two runs determined by GC analysis. [d] Fraction bp 40-60 °C (in all runs). [e] After 1 h at 25 °C.

Table II. Reaction of β-Thujone with *n*-Butyllithium

entry	R[a]	solvent	temp,[b] °C	react time, h	yield,[c] %
1	1:2	ligroin[d]	25	1	91
2	1:2	ligroin	50	1[e]	85
3	1:5	ligroin	25	1	93
4	1:5	ligroin	50	1[e]	89

[a] Thujone:BuLi molar ratio. The thujone solution was added to the BuLi solution. [b] The addition was always carried out at 0 °C, and then the reaction mixture was heated to the stated temp. [c] Average of at least two runs determined by GC analysis. [d] Fraction bp 40-60 °C (in all runs). [e] After 1 h at 25 °C.

Structures of compounds 1 and 2 are fully characterized by their physical properties[1] and NMR spectra.[6] In the present work two series of reactions have been carried out with butyllithium: Table I shows the results of the reactions performed with a mixture mainly constituted by 1 (81.5% 1 and 18.5% 2) and Table II shows the reactions of pure 2. Several variables, such as substrate:reagent ratio, temperature, solvent, time of reaction, etc., have been examined to find out the optimun reaction conditions. Comparison between Tables I and II reveals that pure 2 gives higher yield than the mixture rich in compound 1. GLC-MS analysis of the reaction mixture of Table I indicates that the three reaction products are isomeric ter-

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[1] Guenther, E. "The Essential Oils"; Van Nostrand: New York, 1943, Vol II, p 423.

[2] Kutney, J. P.; Singh, A. K. *Can. J. Chem.* **1982**, *60*, 1842. Kutney, J. P.; Balsevich, J.; Grice, P. *Ibid.* **1980**, *58*, 2461.

[3] Kutney, J. P.; Grice, P.; Pascoe, K. O.; Piotrowska, K.; Retting, S. J.; Szykula, J.; Trotter, J. *Helv. Chim. Acta* **1980**, *65*, 2345.

[4] For a recent review on organometallic addition to carbonyl see: Ashby, E. C.; Laemmle, J. T. *Chem. Rev.* **1975**, *75*, 521.

[5] (a) Nudelman, N. S.; Vitale, A. *J. Org. Chem.* **1981**, *46*, 4625. (b) Nudelman, N. S.; Outumuro, P. *Ibid.* **1982**, *47*, 4347. (c) Nudelman, N. S.; Pérez, D. *Ibid.* **1983**, *49*, 134.

[6] Tori, K. *Chem. Pharm. Bull. Jpn.* **1964**, *12*, 1439.

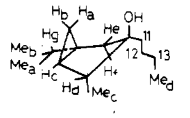
0022-3263/84/1949-1540$01.50/0

Table III. Reaction of Thujone (81.5% 1 and 18.5% 2) with Phenyllithium

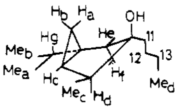
entry	R[a]	solvent	temp,[b] °C	react time, min	yield,[c] %
1	1:2	Et_2O	17	5	86
2	1:2	Et_2O	17	60	89.5
3	1:2	THF	17	5	80.9
4	1:2	THF	17	60	78
5	1:2	THF	50	5	78.8
6	1:2	THF	50	60	76.6
7	1:2	THF-HMPT (20:1)	50	5	67.4
8	1:2	THF-HMPT (20:1)	50	60	65.3

[a] Thujone:Phenyllithium molar ratio. The thujone solution was added to the Phenyllithium solution. [b] The addition was always carried out at 0 °C, and then the reaction mixture was heated to the stated temp. [c] Average of at least two runs determined by GC analysis.

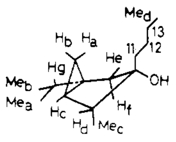
tiary alcohols and that the only additional compound is the original substrate. Careful GLC analysis shows that the three thujols (3–5) are present in the percentages 56.3%, 25.4%, and 18.3%, respectively. Preparative GLC allows the isolation of thujols 3, 4, and 5 which were identified by IR and NMR spectroscopy[7] and elemental analyses.



3-butylneothujol (3)

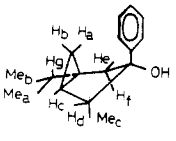


3-butylneoisothujol (4)



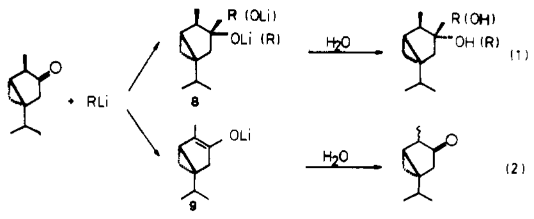
3-butylthujol (5)

Table III shows the results of the reaction of thujone (81.5% 1 and 18.5% 2) with phenyllithium to produce 3-phenylthujol. A wider range of solvent polarity was examined in this reaction, and it can be observed that the yield decreases with increasing polarity of the medium. The reaction is fast, being almost complete in 5 min, and no considerable improvement is achieved by longer reaction periods. Preparative GLC could not be used in the present reaction to isolate the reaction products since a variable degree of dehydration occurs producing considerable amounts of 3-phenyl-β-thujene (6). The products were then separated by succesive preparative TLC. Quantitative and spectroscopic analyses revealed that the main product is largely 3-phenylthujol (7) (R_f 0.59). Two other products were isolated in very small amounts; one of them (R_f 0.26) showed aromatic signals in the NMR spectrum but its quantity was too small to allow accurate structural assignments. The other product (R_f 0.91) did not contain aromatic protons and it might be a thujone anion coupling product.



3-phenylthujol (7)

Scheme I



Discussion

Thujone is an enolizable ketone and it can be expected a priori that besides the desired addition product shown in reaction 1 (Scheme I) some degree of enolization can occur according to reaction 2. This explains why the addition reaction is never complete with enolizable ketones and the highest yields obtained are around 75–90%.[9]

Enolization can also occur by a further reaction of the remaining thujone with the anion addition intermediate 8; to avoid this reaction the lithium reagent was always in excess and the thujone was added to the lithium reagent solution. In the present work the highest yields obtained with butyllithium were 87% (Table I) and 93% (Table II) with the mixture of 1 plus 2 and pure 2, respectively.

Phenyllithium afforded almost a 90% yield (Table III) of the tertiary alcohol from the mixture.

That the residual thujone found in all cases was not due to incomplete reaction is shown by the relatively small effects of using a larger excess of lithium reagent (a 1:5 ratio for entries 4 and 5 compared with a 1:2 ratio for entries for 1–3 in Table I and 1 and 2 in Table II). A similar conclusion can be achieved by analysing the effect of increasing the temperature of the reaction (entries 1 vs. 3 and 4 vs. 5 in Table I, entries 1 vs. 2 and 3 vs. 4 in Table II, and entries 3 vs. 5 and 4 vs. 6 in Table III), the time of reaction (entries 1 vs. 2, 3 vs. 4, and 5 vs. 6 in Table III), or both. Conversely to the expected effect, if the reaction were incomplete, in almost all of the cases a small slight decrease in yield is observed for increased temperature or longer reaction periods, which we attribute to slow condensation reactions of 8, 9, or both giving rise to undetectable condensation byproducts.

One of the outstanding features revealed by the data is the clean reactions observed under the described reaction conditions; none of the common undesirable reduction and/or condensation byproducts[9] occur in measurable amounts and the addition product is contaminated only by the starting thujone.

Butyllithium is known to be hexameric in cyclohexane solution[10] even in dilute concentrations;[11] since the large aggregates should conspire against addition toward the highly constrained structure of thujone the effect of adding an electron-donating solvent, in which the butyllithium is known to be tetrameric[12], was examined. It was found that the increase in the polarity of the solvent produces a considerable *decrease* in the yield (Table I). A wider

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[7] By addition of D_2O and the shift reagent Eu(fod)$_3$. In the case of thujol there is not a satisfactory shift by the addition of Eu(fod)$_3$ but the structure could be fully characterized by comparison of this ^{13}C NMR spectra with data from the literature.[8]

[8] Bolhmann, F,; Zeisberg, R.; Klein, K. *Org. Magn. Res.* **1975**, *7*, 431.

[9] Buhler, J. D. *J. Org. Chem.* **1973**, *38*, 904.

[10] (a) Dunkin, D. B.; Fehsenfeld, F. C.; Schemeltekopf, A. L.; Ferguson, E. E. *J. Chem. Phys.* **1968**, *49*, 1365. (b) Ferguson, E. E.; Fehsenfeld, F. C.; Schemeltekopf, A. L. *Adv. At. Mol. Phys.* **1968**, *5*, 1.

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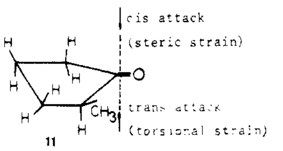
[12] West, P.; Purmort, J. I.; Mc Kinley, S. V. *J. Am. Chem. Soc.* **1968**, *90*, 797.

solvent polarity range is displayed in the reactions of Table III. Since phenyllithium is insoluble in aliphatic hydrocarbons, the reactions were studied in electron-donor solvents. It can be observed in Table III that the yield again decreases considerably by an increase in the polarity[13] (or dipolarity)[14] of the medium. That this is not due to a diminished reactivity of the depolymerized aggregate is shown by the fact that phenyllithium is dimeric in both ethyl ether[15] and THF,[16] but in this last solvent the yield is smaller than in ethyl ether. The keto enol equilibrium should be favored in the more polar solvents and the ionic character of the C–Li bond should be increased by the same media; both effects should give rise to an increase in the enol content of anion **9** and a consequent decrease in the yield of the desired tertiary alcohol.

Theories regarding the stereochemistry of the organolithium reagent addition assume that an entering group R approaches the carbonyl carbon on a line perpendicular to the plane of the carbonyl group.[4] Examination of the different theories seems to favor Cherest and Felkins's[17] approach which considered the stereoselectivity of organometallic compound addition to cyclohexanones to be influenced by two factors: (1) the steric interaction of the incoming group with the 3,5-axial substituents and (2) the torsional strain between the forming C–R bond and the 2,6-axial bonds. Similar considerations are applied to cyclopentanones,[4] as is shown for 2-methylcyclopentanone (**11**).



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1 and **2** show "quasi-boat" conformations to avoid the interactions that H_a should have with H_d and H_e in the "quasi-chair" conformation of **1** and with the C_4 methyl group and H_e in the "quasi-chair" conformation of **2**. But these "quasi-boat" conformations present a severely hindered face to the axial attack; the bridgehead C_6 must occupy a "pseudoaxial" position thus leading to significant steric hindrance. Since this effect surpasses the torsional strain, attack from the α-side prevails as is shown by the data of Table I and II.[18] In fact, compound **2** (Table II), where the α-face is even less hindered, renders higher overall yield than the mixture mainly constituted by isomer **1** (Table I). The same conclusion can be reached by considering the isomer distributions of the products in the reaction with the mixture.

It can be easily deduced that compound **1** suffers ca. 76% attack from the α-face and 24% attack from the β-side. In addition to the torsional strain between the forming bond from the α-face and the C_4–CH_3 bond in compound **1** an additional steric strain to the attack from the α-face arises from the proximity of one of the methyl hydrogens to the entering reagent, which is responsible for a certain amount of attack from the β-face to be observed.

In compound **2**, by the contrary, the β-methyl group introduces a pseudoaxial hydrogen which increases hindrance to the cis attack. The substituents at C_4 (pseudoequatorial methyl) and at C_1–C_5 (pseudoaxial cyclopropane ring) in compound **2** encounter such a severe strain with BuLi attempting to enter the molecule from the β-face that essentially 100% α-attack is observed and no compound arising from a β-attack is detected. Preferential attack from the least hindered side (trans) was previously observed in the alkyllithium additions to 2-methylcyclopentanone;[19,20] in that case the cis-alcohol is produced predominantly but varying amounts (15–30%) of the trans-alcohol are also obtained.

For R = Ph an essentially different stereocontrol is observed. In spite of the fact that the reactions have to be performed in electron-donor solvents high yields are obtained (Table III). In principle, they could be ascribed to the lesser degree of aggregation of phenyllithium when compared with BuLi. But the fact that little change in the isomer ratio occurs with a change of concentration in the RLi reagent suggests that monomeric RLi is the reactive species regardless of the association of the reagent.[21]

Therefore the higher yields obtained for R = Ph should be due to a higher reactivity of the phenyl anion, to the flatness of the phenyl ring which could make attack less hindered, or to a change in mechanism. The most outstanding feature of this reaction is that attack from the most hindered face is practically the only one detected, similarly to the reaction of phenyllithium with 2-norbornanone[22] or with 4-*tert*-butylcyclohexanone,[20,23] where axial entry is preferred against the equatorial preference of alkyl groups. By the contrary, addition to 2-methylcyclopentanone exhibits steric approach control and 95% of the cis-alcohol is obtained.[24]

In the present ketones, more severe steric hindrance to the PhLi attack from the β-face occurs and cannot be reduced by the phenyl ring entering parallel to the 1,5-substituents because of the presence of the cyclopropane ring. Concomitantly, torsional strain in the α-face is also very important. But the situation changes considerably if a late transition state is considered in which the carbonyl carbon atom adopts a "quasi-sp^3" configuration. In that case, the plane of attack rotates ca. 50° clockwise, the PhLi approach from the β-side finds almost no steric resistance, and the torsional strain from the α-face is more important that in a "normal" transition state. Maximun overlap with the phenyl orbitals occurs in this four-center transition state, which is similar to a recently proposed transition state for the phenyllithium addition to carbon monoxide.[25] This could explain the surprising almost exclusive attack from the β-face.

Experimental Section

General Procedure. All reactions involving organometallic reagents were executed under an atmosphere of dry nitrogen using oven vacum-dried glassware and standard techniques for the

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[17] (a) Cherest, M.; Felkin, H. *Tetrahedron Lett.* **1971**, 383; *Ibid.* **1968**, 2205. (b) Cherest, M.; Felkin, H.; Frajerman, C. *Tetrahedron Lett.* **1971**, 379.

[18] Since the alcohol isomer ratios were found to be independent of the reactant ratios and concentrations in all the instances where these factors were investigated,[4] the reaction conditions that give rise to the highest yield were chosen to study the stereochemical course of the reaction (entry 4 of Table I).

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manipulation of air sensitive compounds.[26] IR spectra were determined as film on a Perkin-Elmer F21 infrarred recording spectrophotometer. ^{1}H NMR spectra were determined in a Varian A60 instrument. ^{13}C NMR spectra were determined on a Varian FT-80A. Mass spectra were determined on a Varian Mat CH 7 mass spectrometer. GC–MS were obtained by a Varian 1440 Gas Chromatograph coupled to the Varian Mat CH 7, equipped with a Varian Mat Data System 166. Analytical GLC was done in a Hewlett Packard 5840 instrument using 0.25 in × 12 ft columns on 60/80 mesh with 2% OV-101 on chromosorb W and Carbowax 20 M on chromosorb W in a programmed-temperature manner. Preparative GC was done on a chromatograph designed and built up at the IPNAYS using columns of 15% Carbowax 20 M on chromosorb W. Preparative TLC was carried out in 5-mm thick kieselgel plates using 10% ethyl ether–ligroin as solvent.

Solvents and Reagents. Ligroin (bp 40–60 °C) was refluxed with fresh sulfuric acid, distilled, treated with sodium hydroxide lentils, and then distilled. Tetrahydrofuran (THF) was treated several days with fresh sodium hydroxide lentils, distilled, and kept over sodium benzophenone ketyl. Ethyl ether, free from peroxides,[27] was dried with calcium chloride 12 h, distilled, and kept over sodium wire. All solvents were stored under dried nitrogen atmosphere in special vessels which allow delivery without air contamination and were distilled from sodium benzophenone ketyl solution prior to use. Hexamethyl phosphorus triamide (HMPA) was used without further purification. High purity *n*-butyllithium was prepared by metallation of butyl chloride with lithium wire in ligroin by a procedure already described.[28] Its concentration was determined by a double titration method. The reagent solution was kept in the refrigerator and they were discharged when the residual base exceded 10%. Phenyllithium was prepared by metal–halogen exchange from butyllithium in ligroin and iodobenzene following a procedure previously described.[28,29] Dried crystals, stored in the refrigerator, were dissolved in the desired solvent inmediately before use and the solution valorated by double titration. The mixture of **1** and **2** and pure **2** were obtained from the essential oil of *Aloysia polystachia* by the following sequence: extraction of acids and phenols, extraction of α,β-unsaturated ketones by Tiemman's method, and extraction of other undesirable aldehydes and ketones by bisulfite adduct.[30] The essential oil freed of the compounds cited above was vacuum distilled; the fraction with bp 69–72 °C (16 mmHg) renders a semicarbazone of mp 186.5–188.5 °C (lit.[1] 186–188 °C). Treatment of the semicarbazone with phtalic anhydride[31] afforded a mixture of **1** and **2** with the isomer ratio determined by optical rotation $\alpha^{20}{}_D$ −2.80 (81.5% of **1** and 18.5% of **2**). Pure **2** was obtained from the above mixture in two steps: epimerization with sodium ethoxide in ethanol afforded a mixture (35% **1** and 65% **2**) from which β-thujone (**2**) was isolated by the procedure of Eastman and Winn.[30] Distillation at reduced pressure afforded pure **2**: bp 63–64 °C (5 mmHg); $\eta^{20}{}_D$ 1.4528; $d^{20}{}_4$ 0.9180; $\alpha^{20}{}_D$ +64.4.

Reaction with Organolithium Reagents. *n*-Butyllithium. Into a test tube capped with a nonair stopper containing a solution (0.7 N) of the organolithium reagent (6 mL, 4.2 mmol for 1:2 runs or 8 mL, 5.6 mmol for 1:5 runs) in the desired solvent and a nitrogen atmosphere was added a solution of 0.35 mL (2.1 mmol) of thujone in 3 mL of the working solvent (1:2) or 0.19 mL (1.18 m.mol) of thujone in 1 mL of the working solvent (1:5) dropwise at 0 °C with continuous stirring.

Phenyllithium. To 6 mL of a solution (0.67 N) of the reagent (4.02 mmol) in the desired solvent contained in a tube as described above was added dropwise a solution of 0.33 mL (2 mmol) of thujone under the conditions just mentioned for *n*-butyllithium. Each reaction mixture was allowed to react under the conditions listed in Tables I–III and quenched with a saturated solution of aqueous ammonium chloride. When the solvent of the reaction is insoluble in water, the organic compounds were extrated with ligroin and dried ($MgSO_4$) and the mixture was analyzed by GLC.

Spectral Characteristics and Elemental Analyses of Compounds 3–7. Proton assignments were helped by the europium(III) induced chemical shift method[32,33] using Eu(fod)$_3$-d_{27} as shift reagent.[34] The conformational assignment in the thujols was made by quantitation of the chemical shift induced by continuosly increasing amounts of Eu(fod)$_3$-d_{27} added.[34]

3-Butylneothujol (3): IR (film) ν (cm^{-1}) 3680 (m), 3580 (m), 3080 (m), 2980 (s), 2920 (s), 1470 (s), 1440 (m), 1385 (m), 1370 (m), 1255 (m), 1160 (m), 1110 (m), 992 (m), 975 (s), 912 (m), 846 (m), 813 (m); ^{1}H NMR (Cl_4C) δ 1.90 (d) and 1.86 (d) (J_{gem} = 14, H_e and H_f), 1.32 (q, J_{Me_c} = 6, H_d, no coupling between H_d and H_c indicates a dihedral angle of 90°), 1.28 (br, comp, (C_{11}, C_{12} and C_{13})), 1.06 (d, J_{H_d} = 7, Me_c), 1.03 (d, J_{H_g} = 7, Me_a or Me_b), 1.00 (s, –OH, dissapears with D_2O), 0.95 (ca. t, Me_d), 0.92 (d, J_{H_g} = 7, Me_a or Me_b), 0.56 (comp, H_a and H_b). Anal. Calcd for $C_{14}H_{26}O$: 80.00, C; 12.38, H. Found: 80.01, C; 12.50, H.

3-Butylneoisothujol (4): IR (film) ν (cm^{-1}) 3620 (m), 3580 (m), 3080 (m), 2920 (s), 1470 (s), 1440 (m), 1386 (m), 1370 (m), 1255 (m), 1240 (m), 1150 (m), 1115 (m), 1060 (w), 1045 (m), 1020 (m), 995 (s), 910 (m), 870 (m), 815 (m); ^{1}H NMR (Cl_4C) δ 1.98 (q d, J_{Me_c} = 7, J_{H_c} = 3, H_d, H_c, H_d dihedral angle 50°), 1.84 (d) and 1.82 (d) (J_{gem} = 14, H_e and H_f), 1.30 (s, –OH, dissapears with D_2O), 1.29 (br, comp. (C_{11}, C_{12} and C_{13})), 1.08 (d, J_{H_d} = 6, Me_c), 0.92 (d, J_{H_g} = 7, Me_a or Me_b), 0.90 (ca. t, Me_d), 0.88 (d, J_{H_g} = 7, Me_b or Me_a), 0.60 (comp, H_a and H_b). Anal. Calcd for $C_{14}H_{26}O$: 80.00, C; 12.38, H. Found: 80.11, C; 12.55, H.

3-Butylthujol (5): IR (film) ν (cm^{-1}), 3640 (m), 3500 (s), 2980 (s), 1470 (s), 1440 (m), 1385 (m), 1370 (m), 1255 (m), 1225 (m), 1200 (m), 1160 (m), 1135 (m), 1110 (m), 1058 (m), 1037 (m), 1020 (m), 1000 (s), 900 (m), 883 (m), 856 (m), 807 (m); ^{1}H NMR (Cl_4C) δ 1.90 (q, J_{Me_c} = 7, H_d, H_d, H_c dihedral angle 90°), 1.69 (d) and 1.63 (d) (J_{gem} = 12, H_e and H_f), 1.30 (comp. (C_{11}, C_{12} and C_{13})), 1.10 (d, J_{H_d} = 7, Me_c), 1.05 (s, –OH, dissapears with D_2O), 0.90 (d, J_{H_g} = 6, Me_a or Me_b), 0.88 (ca. t, Me_d), 0.86 (d, J_{H_g} = 6, Me_b or Me_a), 0.66 (comp., H_a and H_b); ^{13}C NMR δ 83.73 (C_3), 46.39 (C_4), 39.96 (C_2), 39.14 (C_{11}), 33.30 (C_7), 33.23 (C_1), 30.44 (C_5), 26.20 (C_{12}), 23.24 (C_{13}), 20.07 (C_8), 19.95 (C_9), 18.69 (C_{14}), 16.58 (C_{10}), 14.06 (C_6). Anal. Calcd for $C_{14}H_{26}O$: 80.00, C; 12.38, H. Found: 80.09, C; 12.51, H.

3-Phenyl-β-thujene (6): IR (Cl_4C) ν (cm^{-1}) 3080 (m), 3015 (s), 2980 (m), 2920 (m), 1620 (w), 1605 (m), 1582 (w), 1500 (m), 1460 (m), 1385 (m), 1370 (m), 1260 (m), 1058 (m), 1025 (m), 945 (m), 875 (m), 840 (m), 692 (s); ^{1}H NMR (Cl_4C) δ 7.2 (comp, phenyl H), 6.12 (s, H_e), 2.99 (q d, J_{Me_c} = 7, J_{H_c} = 2, H_d, H_c, H_d dihedral angle 110°), 1.1 (d, J_{H_d} = 7, Me_c), 1.05 (d, J_{H_g} = 6.5) and 0.90 (d, J_{H_g} = 7, Me_a and Me_b), 0.63 (comp, H_a and H_b).

3-Phenylthujol (7): IR (film) ν (cm^{-1}) 3650 (m), 3580 (m), 3040 (m), 2980 (s), 2870 (w), 1605 (m), 1495 (m), 1450 (s), 1385 (s), 1368 (s), 1175 (m), 1160 (m), 1115 (w), 1090 (w), 1075 (w), 1055 (m), 1040 (m), 982 (m), 910 (m), 885 (m), 848 (m), 810 (m), 762 (s), 700 (s); ^{1}H NMR (Cl_4C Cl_3CD) δ 7.25 (comp, phenyl H), 3.70 (s, –OH, dissapears with D_2O), 2.13 (d) and 2.05 (d) (J_{gem} = 13.5, H_e and H_f), 1.85 (q, J_{Me_c} = 7, H_d, H_c, H_d dihedral angle 90°), 1.37 (comp, H_g), 1.20 (s, H_c), 0.96 (d, J_{H_g} = 5.5, Me_a or Me_b), 0.87 (d, J_{H_d} = 5.5, Me_c), 0.80 (d, J_{H_g} = 5.5, Me_b or Me_a), 0.42 (comp, H_a and H_b). Anal. Calcd for $C_{16}H_{22}O$: 83.47, C; 9.57, H. Found: 83.31, C; 9.76, H.

GLC–MS of the Reaction Mixtures. GLC–MS analysis of the reaction mixtures gave the following MS for the main reaction products: reaction with *n*-butyllithium, *m/e* (% relative intensity) 195 ($M^+ - 15$, 0.7), 192 ($M^+ - 18$, 4.1), 167 (12), 149 (4.8), 135 (15.4), 110 (58.2), 95 (79), 85 (56.8), 57 (100), 43 (60.2), 41 (84.7); reaction with phenyllithium, *m/e* (% relative intensity) 230 (M^+, 6.5), 215 (0.9), 212 (3.9), 187 (25.2), 153 (2.6), 135 (2.3), 105 (100), 95 (61.9), 67 (85.7), 43 (45.6).

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Registry No. 1, 546-80-5; 2, 471-15-8; 3, 88904-61-4; 4, 88904-62-5; 5, 88904-63-6; 6, 88904-64-7; 7, 88930-40-9; BuLi, 109-72-8; PhLi, 591-51-5.

Metal-Ammonia Ring Reduction of Aromatic Carboxylic Acid Esters

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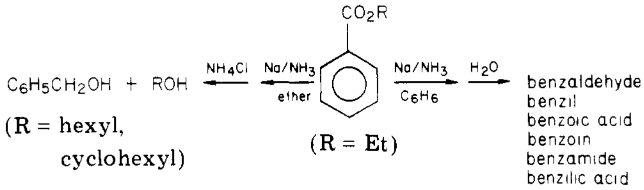
Although esters are often reduced to alcohols with metal-ammonia solutions, it has been found that aromatic carboxylic acid esters can be reduced efficiently to the corresponding dihydro aromatics when 1.25 equiv of water is present before metal addition. The general effect of the presence of water (before metal addition) upon metal-ammonia reduction of polycyclics was tested with anthracene (0.5 g), which was reduced to 9,10-dihydroanthracene (97% yield) in the presence of 3.5 g of water. Polynuclear aromatic esters are reduced smoothly by this technique, but in the absence of water, alkyl 9-anthroates gave a dimer assigned as axial/axial on the basis of nuclear Overhauser enhancements. Possible mechanistic pathways for dimer formation were investigated by the addition of 9,10-dihydroanthracene monoanion as well as anthracene dianion to ammonia/THF solutions of ethyl anthroate. This led to dimer and trimer formation, respectively. The structures of these compounds are discussed in light of their carbon and proton NMR spectra.

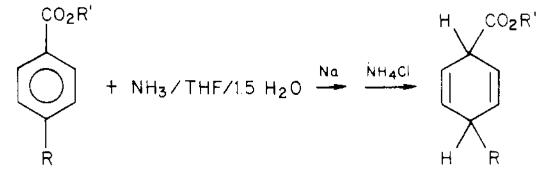
The reduction of esters to alcohols by alkali metals and alcohol in liquid ammonia is a familiar process known as the Bouveault-Blanc procedure.[1a] These same reagents, under appropriate conditions, can also effect the ring reduction of aromatic compounds in a useful reaction generally known as Birch reduction.[1] Hence treatment of aryl carboxylic acid esters with metal/ammonia solutions is potentially complex. In fact, Kharasch et al.[2] investigated the reaction of ethyl benzoate with $Na/NH_3/C_6H_6$ and found a variety of products all involving reduction of the carbonyl group and/or cleavage of the alkyl portion of the ester. Moreover, the presence of benzamide suggests susceptibility of the carbonyl group to nucleophilic attack by ammonia (or amide) in addition to reduction processes. More recently, the efficient (78-97% isolated yields) conversion of several different benzoate esters to alcohols using sodium/ammonia solutions has also been reported.[3]



(R = hexyl, cyclohexyl)

(R = Et)

In view of these results, the ring reduction of aryl carboxylic acid esters appeared quite challenging but nonetheless was of interest to us since (1) we have found dihydroaromatic esters to be more resistant to isomerization, rearomatization, etc., than the corresponding acids and (2) we hoped that the carboalkoxy group might show enhanced activation properties, since acids are necessarily present as carboxylate anions in ammonia solution providing an additional negative charge. Not unexpectedly, our initial experiments with benzoate esters met with failure. However, in a somewhat serendipitous manner we found that ring reduction of ethyl benzoate can be effected almost quantitatively when water (ca. 1.5 equiv) is present *before* the addition of metal.[4] This is, of course, rather unusual since metal/ammonia reductions are usually carried out with the rigorous exclusion of water, although alcohols are often used as cosolvents for the reduction of benzene derivatives.[1] Generally, we have not found alcohols to be as satisfactory as water, but, in any event, the key to our procedure is the presence of the proton source *before* the addition of metal.



R = H, Me; R' = Et, *t*-Bu

Electron addition to the benzoate esters must occur much faster than destruction of the metal by water since we employ only a slight excess of sodium. The likely role of the water is rapid protonation of the radical anion 1 before such processes as dimerization or ester cleavage may occur. The (delocalized) anion 2 appears resistant to further electron addition as well as reaction with any nucleophiles that may be present. Similarly, the starting esters are unaffected by liquid ammonia (at least for short

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