mophenyl disulfide (147 mg), methyl 4-bromophenylthioacetate (95 mg), and recovered starting material (90 mg). No evidence of reaction with toluene was found even in the NMR of the crude product.

Thermolysis of 8 in Anisole. A solution of **8** (1 g, 0.0038 mol) in anisole (20 mL) was refluxed for 4 h. The residue remaining after evaporation of excess anisole in vacuo was chromatographed on SiO_2 (3 × 18 cm) and eluted with hexane (3 L), and then with 5% $CHCl_3$ in hexane (10 L). Collection of 250-mL fractions gave diphenyl disulfide (0.2 g, fractions 3–29) and **13** (0.4 g, 28%, fractions 40–45): mp 71.5–72.5 °C (C_2H_5OH); IR 1680 1585, 1260 cm^{-1}; NMR δ 8.00–7.75 (2 H, d, J = 8 Hz), 7.45–7.15 (9 H, m), 6.95–6.70 (2 H, d, J = 8 Hz), 5.75 (1 H, s), 3.72 (3 H, s); MS (70 eV), m/e 368 ($M^{+\cdot}$), 229 (100%). Anal. Calcd for $C_{21}H_{17}ClO_2S$: C, 68.4; H, 4.7. Found: C, 68.8; H, 4.5.

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Registry No.—**1**, 63215-96-3; **3**, 63215-97-4; **4**, 6275-26-9; **5**, 63215-98-5; **6**, 63215-99-6; **7**, 63216-00-2; **8**, 58936-71-3; **9**, 63216-01-3; **11**, 63216-02-4; **12**, 63216-03-5; 4-bromophenylthioacetonitrile, 50837-23-5; methyl 4-bromophenylthioacetate, 50397-69-8; ω-phenylthio-4-chloroacetophenone, 33192-00-6; 2-carboxamidophenyl benzyl sulfide, 54705-18-9; 2-cyanophenyl benzyl sulfide, 63216-04-6; **11** ortho isomer, 63216-05-7; 4-bromophenyl disulfide, 5335-84-2; 4-bromobenzenethiol, 106-53-6; benzenethiol, 108-98-5.

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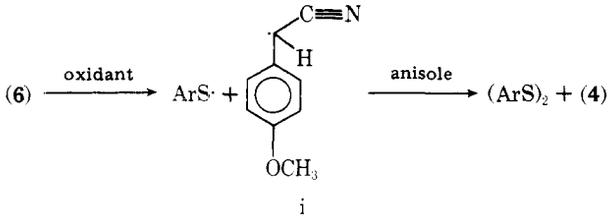
(12) Compounds **5** and **6** are quantitatively recovered after prolonged (24 h) reflux in anisole alone or anisole containing a molar excess of *p*-toluenesulfonic acid. The formation of **4** via a sequence of sulfur protonation in **6** followed by loss of *p*-bromobenzenethiol and electrophilic attack on anisole by the resultant carbocation is therefore untenable. An alternative process involves conversion of **6** into **i** followed by free radical attack on anisole. Due to the scale of the reaction, other isomers of **4**, though



i

probably formed, were present in quantities too small to detect. The oxidant in this reaction would be unreacted **1**; sulfoxides are known oxidants (ref 10). Using *m*-chloroperbenzoic acid (CH_2Cl_2) as the oxidant, the sulfoxide of **6** and 2,3-di(4-methoxyphenyl)succinonitrile, the coupling product of **i**, were isolated. Formation of **i** appears to be quite facile; in the presence of anisole **4** forms, but in the absence of a reactive solvent **i** dimerizes.

(13) The mode of formation of *p*-chlorobenzoic acid is unknown. In the presence of moisture a retro-Claisen condensation could convert **8** into *p*-chlorobenzoic acid and methyl phenyl sulfoxide. The latter product was not observed however. One could speculate that *p*-chlorobenzoic acid arises from decomposition of the hemihydrate of *p*-chlorophenylglyoxal, the expected Pummerer rearrangement product from **8** in acid solution in the presence of fortuitous water (ref 14).

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Determination of the Rate of Reduction of Benzophenone-*1*-^{14}C by Lithium Benzhydrolate

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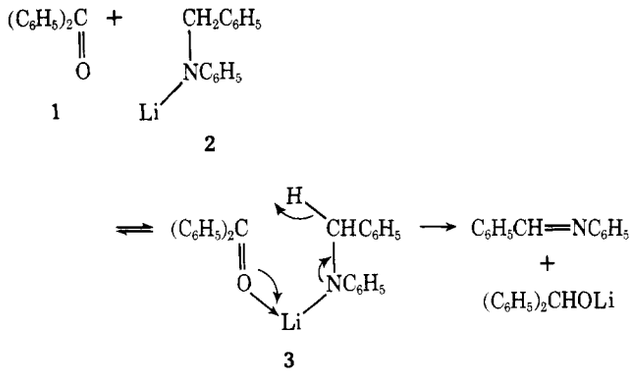
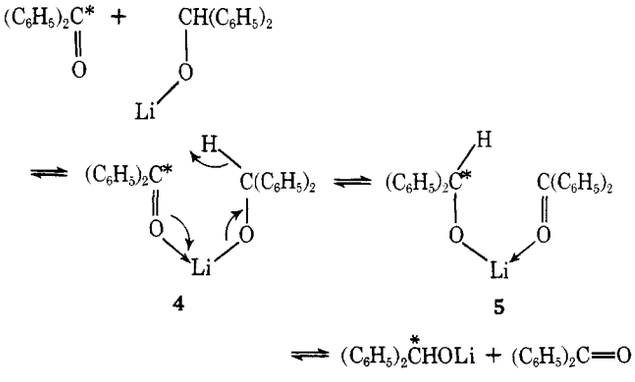
In previous work concerning the properties of N-metalated secondary amines as hydride donors, Wittig and co-workers[2,3] found that lithium *N*-benzylanilide (**2**) effected a reduction of ketones [e.g., benzophenone (**1**)] to yield corresponding lithium alcoholates and Schiff bases. On the basis of kinetic studies, the authors proposed that a rapid equilibrium was established between starting materials and a 1:1 "ate complex"[4] (**3**), and that hydride transfer occurred in a subsequent



irreversible rate-determining step. The reaction was found to be second order, being first order with respect to each reactant.

In view of these results, it was of interest to investigate the nature of the reduction between an analogous O-metalated alcohol, benzhydrol, and benzophenone. Of special interest was the determination of the rate of the carbinol–carbonyl equilibrium for comparison to that of the N-metalated amine/benzophenone system. It was thought that the reaction would proceed via rapid formation of an ate complex (**4**), slow transfer of hydride to form a new ate complex (**5**), and, finally, rapid equilibration to form products. Similar mechanisms involving cyclic intermediates such as **4** and **5** have been



generally adopted for both Grignard[5] and Meerwein–Ponndorf–Verley (MPV)[6] reductions. Further, it has been established that hydrogen transfer takes place directly from metalated component to ketone in these reactions.[5,7]

In this study, radioactive benzophenone-*1*-^{14}C was allowed to react with inactive benzhydrol in tetrahydrofuran (THF) at 90 °C. At various time intervals, the reaction was quenched

Table I. Increase in Radioactivity of Benzhydrol with Time

Run	Time, s, $\times 10^{-3}$	Benzhydrol-*1*-^{14}C, mg, per 50-mg sample[a]
1	5.4	5.50
	12	7.50
2	12	7.38
	24	12.75
	48	19.38
3	9	6.12
	12	7.28
	15	8.62
	18	10.25
	24	12.38
	36	15.50
	42	17.12

[a] The infinity value for benzhydrol-*1*-^{14}C per 50-mg sample was taken to be 25.28 mg (50 mmol).

by hydrolysis and the products were separated by column chromatography. Both the decrease of radioactivity in benzophenone and the increase of radioactivity in benzhydrol were determined by liquid scintillation counting methods.

Systematic monitoring of the products by thin-layer chromatography indicated the absence of by-product formation during the reaction. Thus, for example, formation of benzpinacol, which occurs in photolysis reactions between ketone and benzhydrol,[8] was not observed. It is known that condensation and enolization reactions do not occur with benzophenone.[5]

The intermediacy of free radicals or of radical anions was not expected on the basis of previous findings of Doering and Aschner[7] and of Russell et al.[9] In the former work, an alcoholate-catalyzed MPV reduction was unaffected when carried out in the presence of radical inhibitors. In the latter work, only trace quantities of radicals were observed in a reaction between benzophenone and benzhydrol in 80% Me_2SO/20% *tert*-butyl alcohol with an excess of potassium *tert*-butoxide, conditions much more favorable to radical anion formation than those used in this study.

Data obtained for the increase of radioactivity in benzhydrol as a function of time are found in Table I. From the slope of the plot of log $[1 - (x/x_\infty)]$ vs. time (see Experimental Section), a rate of exchange, R, of 1.51×10^6 s^{-1} (9.06×10^{-5} min^{-1}) was determined for the reaction. Regardless of the actual kinetics of the exchange reaction, the rate of appearance of radioactivity in benzhydrol is first order with respect to radioactivity.[10] Although the data do not permit the conclusion that the reaction is second order, this molecularity is expected based on the similarity of the reaction to the lithium *N*-benzylanilide reduction. In contrast, an MPV reduction involving ketone and aluminum alcoholate is more complex, being first order in ketone but variable order in aluminum alcoholate.[11,12] Under the assumption that the benzophenone/lithium benzhydrolate reduction is indeed second order, a rate constant of 1.51×10^{-4} M^{-1} s^{-1} (9.06×10^{-3} M^{-1} min^{-1}) is obtained.

For the benzophenone/lithium *N*-benzylanilide system in ether at 20 °C, a second-order rate constant (K_2) of 1.67×10^{-2} M^{-1} min^{-1} has been reported.[2] This value of K_2, upon extrapolation of an Arrhenius plot, becomes ca. 5 M^{-1} min^{-1} at 90 °C in ether.[3] The reaction proceeds faster by a factor of 2 in THF.[3] Taking into consideration a statistical factor of 2 (lithium *N*-benzylanilide has two H's β with respect to Li vs. one for lithium benzhydrolate) leads to the result that benzophenone undergoes hydride reduction by lithium *N*-benzylanilide faster than by lithium benzhydrolate by a factor of ca. 500.

This difference in rate can be discussed in terms of the atoms occupying the α and β positions and their substituents. At the β position, the additional phenyl group of the alcoholate would be expected to accelerate release of hydride on the basis of its ability to stabilize incipient positive charge at the β carbon atom. At the α position, the greater electronegativity of the oxygen atom of the alcoholate would be expected to decrease hydride mobility. Apparently this latter effect dominates the former, thus slowing the hydride transfer by the factor observed.

It is also of interest to compare the K_2 value derived from this work with that found in previous investigations of the MPV reduction of deuterated acetone by tetrameric aluminum isopropoxide.[6e] In the MPV system, a K_2 value in benzene of 32.5×10^{-6} M^{-1} s^{-1} is obtained by Arrhenius extrapolation to 90 °C. Thus, only a factor of 5 separates the rate constants of these two reductions. It is possible that this difference can be accounted for on the basis of substituents (phenyls vs. methyls) and solvents (THF vs. benzene) for the two systems, thus suggesting that hydride transfer for a given ketone/alcoholate pair proceeds at similar rates regardless of the metal involved. Such a conclusion would be consistent with the present view that the first step, i.e., ketone–metal coordination, is a rapid and reversible step, followed by rate-determining hydride transfer.

Experimental Section

Solvents and Solutions. All solvents were dried and distilled. Ether was refluxed over sodium metal until the blue color of benzophenone ketyl was observed, then it was distilled and stored over sodium metal. Tetrahydrofuran was shaken with aqueous 50% potassium hydroxide and dried over solid potassium hydroxide, followed by anhydrous calcium chloride. The THF was then refluxed and distilled over sodium metal and stored over lithium aluminum hydride, from which it was freshly distilled prior to use. The scintillation solution was prepared by dissolving 0.4 g of 1,4-bis(2-methyl-5-phenyloxazolyl)benzene and 5.0 g of 2,5-diphenyloxazole in 1 L of dry toluene. For each activity determination, 50 mg of substance was dissolved in 15 mL of this solution.

Benzophenone-*1*-^{14}C. Benzoic acid-*1*-^{14}C (1.7 mg) having a specific activity of 21.3 μCi/mg was diluted with 4.99 g of inactive benzoic acid. This material was converted to benzophenone-*1*-^{14}C by the method described by Murray and Williams.[13] The product, obtained in 65% yield, was recrystallized from petroleum ether (80–90 °) to give pure benzophenone-*1*-^{14}C, mp 47–48 °C, having a specific activity of ca. 5 μCi/g. Dilution of this material (1.08 g) with inactive benzophenone (47 g) gave benzophenone-*1*-^{14}C with a specific activity of ca. 0.1 μCi/g.

Benzhydrol-*1*-^{14}C. This material was obtained from benzophenone-*1*-^{14}C as described by Murray and Williams.[14] Purification of the product was effected by column chromatography (Al_2O_3) and by recrystallization from petroleum ether (80–90 °C). A yield of 1.56 g (65%) of benzhydrol-*1*-^{14}C, mp 68–69 °C, specific activity ca. 0.1 μCi/g, was obtained.

Lithium Benzhydrolate. All operations described below were carried out under an atmosphere of dry nitrogen. In a typical run, benzhydrol (5.0 g, 27 mmol) was dissolved in dry ether (50 mL) and an equimolar amount of methyllithium was added. The solution was stirred for 2 h, during which time crystals of lithium benzhydrolate separated. The crystals were collected on a fritted glass filter, washed three times with dry ether, and dried under vacuum. The material was dissolved in dry THF (100 mL) and the concentration of the resulting solution was determined by removing an aliquot, hydrolyzing, and titrating with 0.1 N hydrochloric acid. In general, the solutions were about 0.14 M in lithium benzhydrolate.

Kinetics. Equimolar amounts of benzophenone-*1*-^{14}C and lithium benzhydrolate were added to dry THF at room temperature so that the solution was 0.1 M in each component. Aliquots (10-mL) of the solution were placed into sealed tubes under dry nitrogen and the tubes were placed into a thermostated bath kept at 90 ± 0.05 °C. At varying time periods, the tubes were removed, the contents quickly cooled, and the reaction quenched by addition of water. THF was removed in a stream of dry nitrogen and the aqueous solution was

extracted with ether. The ethereal extracts were combined, washed with water, and dried over sodium sulfate. A thin-layer chromatogram (Kieselgel G, benzene/CH_2Cl_2, 2/1) confirmed the presence of only two components, benzophenone and benzhydrol. These materials were separated by column chromatography (Al_2O_3) by eluting with cyclohexane (100 mL), carbon tetrachloride (250 mL), benzene (250 mL), and chloroform (300 mL). The appropriate fractions were combined, and the products were recrystallized twice from petroleum ether (80–90 °C). Samples (50-mg) of each of the materials were dissolved in the scintillation solution and the time required for 10^4 impulses was measured. From the time values obtained for each sample, the amount of active benzophenone and/or benzhydrol per 50-mg sample was determined by comparison to previously prepared calibration curves. In all cases, over 95% of the radioactivity could be accounted for. No exchange of carbon-14 was observed under the conditions of chromatographic separation. Three kinetic runs were made in which the reaction was followed through ca. 2 half-lives. These data are presented in Table I.

The rate of carbon-14 exchange, R, for a reaction of the type

$$BX^* + AX \rightleftharpoons AX^* + BX$$

is given by the general expression:[15]

$$R = -\frac{ab}{a+b}\left\{\frac{2.3}{t}\log\left[1-(x/x_\infty)\right]\right\}$$

where a and b = total concentration of AX and BX*, respectively; X = concentration of active AX at time t; and $x_\infty = x$ at t_∞. Under the assumption that the reaction is second order, $K_2 = R/ab = -[2.3/a + b)t]\log[1 - (x/x_\infty)]$.[6e,16] A plot of log $[1 - (x/x_\infty)]$ vs. time was constructed and fitted by the method of least squares (correlation coefficient = 0.987). From the slope, R (and K_2) were evaluated.

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Registry No.—Benzoic acid-*1*-^{14}C, 1589-66-8; benzophenone-*1*-^{14}C, 51594-23-1; benzyhydrol, 91-01-0; lithium benzhydrolate, 2036-66-0; benzhydrol-*1*-^{14}C, 55366-57-9.

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A Simple and Practical Synthesis of Olivetol

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The complete structural elucidation[1,2] of some psychotomimetically active components of marihuana and the extensive biological activity[3] of these components have stimulated interest in the synthesis of cannabinoids.[4–7] The synthesis of these compounds depends largely on the availability of the key intermediate olivetol, 1-*n*-pentyl-3,5-dihydroxybenzene, and homologs. A practical and efficient synthesis which makes these compounds readily available in quantity will considerably facilitate and stimulate further investigation of the synthetic and biological aspects of the cannabinoids.

While several papers on the synthesis of olivetol have appeared recently,[8–10] they did not differ much from the earlier investigations[11,12] in that 3,5-dimethoxybenzoic acid was used as the starting material. This substance is, in fact, expensive and not readily available. In the case where trimethoxy derivatives have been employed,[13] the in situ 4-demethoxylation, as Birch and Slabbe[9] pointed out, results in a poorer quality product. Finally, a recently described synthesis starting from an α,β-unsaturated ester[14] involves complicated steps and has severe steric limitations.

We would like to report a three-step total synthesis[15] of olivetol (**3**) from readily available aliphatic precursors. The α,β-unsaturated ketone[16] **1** was reacted with dimethyl malonate enolate to give the cyclic Michael adduct **2** which was aromatized and subsequently decarbomethoxylated when treated with bromine in DMF, initially at 0 °C[17] and then at refluxing temperature, to yield olivetol in 62% overall yield.

Alternatively, **2** was decarbomethoxylated by successive treatment with alkali and acid to afford the enol **4** which was etherified with methanolic hydrogen bromide to furnish the keto enol ether **5**. Aromatization with etherification[18] of **5** with cupric bromide in methanol gave 1-*n*-pentyl-3,5-dimethoxybenzene (**6**) in an overall yield of 37%. Compound **6** was then demethylated with pyridine hydrochloride to provide 82% of **3**.

Olivetol (**3**) prepared directly by route **1** → **2** → **3** (see Scheme I) is practical and inexpensive. This synthesis is general and suitable for the preparation of homologues of olivetol containing lower or higher or branched alkyl groups (see Table I). This sequence has also been used to incorporate a labeled carbon atom in the aromatic ring.[19]

The alternative route leads to a variety of intermediates which per se could be of synthetic interest. The keto-enol **4**, used originally by adams[20] and co-workers in the synthesis of cannabinol, was laboriously prepared by partial reduction of olivetol.

Experimental Section

All melting points (uncorrected) were taken in open capillary tubes in a Thomas–Hoover melting point apparatus. Vapor phase chromatographs were determined with an F & M Model 810 instrument, using a 4 ft × ¼ in. S.S. column of 3% silicon rubber on Diatoport 5 at 160 °C under helium gas flow of 90 mL/min. Infrared spectra were determined with a Beckman IR-5 infrared spectrophotometer and ultraviolet spectra were measured with a Cary Model 14 M spectro-

Scheme I