

of the products at reduced pressure afforded a volatile fraction which contained 0.40 mmole (10% yield) of dioxane. On addition of ether and 2 ml. of concentrated hydrochloric acid to the residue, a white precipitate of 2-(2-boronophenyl)-benzimidazole hydrochloride, 1.10 g. (87%, calcd. as a monohydrate), m.p. 250–260°, was obtained. Analysis of the ether solution, after concentration, by v.p.c. indicated 1.75 mmoles (45% yield based on chloride ion) of 2-(2-chloroethoxy)-ethanol.

(C).—A mixture containing 1.35 g. of I, 12.6 g. of collidine, 10 ml. of 2-chloroethanol and 20 ml. of 1-butanol was heated at

89° for 181 hr. During this time collidine hydrochloride separated as a crystalline precipitate. The mixture was added to ether and filtered, yielding 14 g. (84%) of collidine hydrochloride, which was identified by its infrared spectrum. The filtrate was concentrated and extracted with dilute hydrochloric acid, and the acid extracts were washed several times with ether. Distillation of the organic and combined ether layers afforded 2.80 g. (21%) of 2-butoxyethanol, b.p. 53–54° (2.7 mm.), n_D^{20} 1.4180 (lit. n_D^{20} 1.4177), identified by its infrared spectrum, and 1.12 of higher boiling residue.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STATE UNIVERSITY OF NEW YORK AT BUFFALO, BUFFALO 14, N. Y.]

Lithium Tetrakis-(N-dihydropyridyl)-aluminate: Structure and Reducing Properties¹

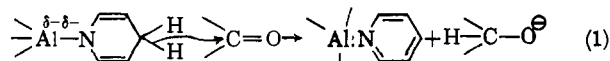
BY PETER T. LANSBURY AND JAMES O. PETERSON

RECEIVED MARCH 7, 1963

The reaction of lithium aluminum hydride with excess pyridine, in the absence of more readily attacked substrates, including aldehydes, ketones, carboxylic acids and their derivatives, results in the formation of lithium tetrakis-(N-dihydropyridyl)-aluminate (I). Solutions of I, as well as the crystalline salt, have been examined by n.m.r. and infrared spectroscopy and found to lack Al-H bonds and to contain both 1,2- and 1,4-dihydropyridine groups bound to aluminum. Compound I reacts with highly electrophilic carbonyl groups by hydrogen transfer from the dihydropyridine moieties. Diaryl ketones react quite rapidly, other ketones sluggishly, and carboxylic acids and esters are essentially unaffected. Several novel selective reductions of bifunctional compounds by I are described.

Introduction

Several years ago we undertook a study of lithium aluminum hydride (LAH) reactions in pyridine solution.² It was anticipated that carbonyl compounds would undergo reduction faster than pyridine solvent,³ if the former were initially present when the hydride was added. As expected, aldehydes, ketones and carboxylic acids and esters are cleanly and rapidly reduced when LAH is added to their pyridine solutions. It was of interest to study the reactions of lithium aluminum salts of dihydropyridines and related compounds, which result from attack of LAH on the heteroaromatic ring, with reducible substrates, since free dihydro-N-heteroaromatic compounds are known to undergo hydrogen transfer to certain organic compounds.⁴ Accordingly, solutions of LAH in pyridine were allowed to interact until no free LAH remained (see below) and carbonyl compounds were then added to the resulting solution which supposedly contained species such as $\text{LiAl}(\text{NR}_2)_4$ (where NR_2 is 1,2- and/or 1,4-dihydropyridyl), by analogy with the reaction of secondary amines with LAH.⁵ It was anticipated that the anionic⁶ dihydropyridine groups in such salts would be more potent hydride donors than the more covalent 1,4-dihydropyridines studied by Westheimer^{4a,b} and Braude.^{4c} We have observed that the anionic complex prepared as described above does



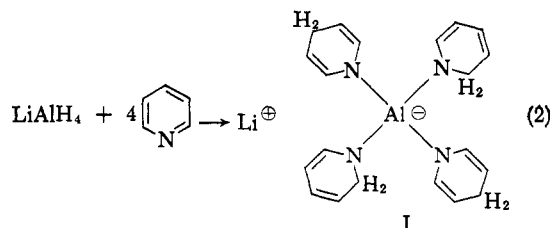
indeed readily reduce certain aldehydes and ketones, but not carboxylic acids and esters,¹ in contrast to the parent LAH. Furthermore, novel selectivity is exhib-

ited toward various types of ketones in that diaryl ketones are reduced with greater ease than other types,¹ which is in the opposite order of reactivities observed in other carbonyl addition reactions.

It is the purpose of this report to present information concerning the preparation and structural features of this novel reducing agent and to describe procedures for its use. In addition, the results of several reductions of bifunctional compounds, where the selectivity of the reagent is used to advantage, are described, and a rationalization of its capabilities is attempted.

Discussion

Lithium tetrakis-(N-dihydropyridyl)-aluminate (I), the responsible reducing agent generated from LAH and pyridine, is generated on a small scale by aging the orange-colored solution (*ca.* 0.25 *M*) for at least 24 hr. in a rubber-capped serum flask (initially at 0°, then at room temperature), from which aliquots can be removed by a hypodermic syringe. Crystalline I is obtained from more concentrated solutions (0.5 *M*) by filtration in a dry box and subsequent vacuum drying. Reproducible C, H, and N analyses could not be obtained, possibly because aluminum and lithium carbides and/or nitrides are formed during combustion, thus resulting in the observed low C and N analyses. Furthermore, reliable analytical results were hampered by the inability to remove all pyridine from I without decomposition. However, compelling evidence for the major structural features in I has been obtained from chemical and physical evidence, as discussed below.



Initial indications that hydrogen transfer to substrate originated from dihydropyridine groups in I came from studies using lithium aluminum deuteride and pyridine.¹ When relatively fresh solutions of these reactants were added to benzophenone and the resultant

(1) For preliminary accounts of portions of this work, see P. T. Lansbury and J. O. Peterson, *J. Am. Chem. Soc.*, **83**, 3537 (1961); **84**, 1756 (1962).

(2) P. T. Lansbury, *ibid.*, **83**, 429 (1961); P. T. Lansbury, J. R. Rogozinski and F. L. Coblenz, *J. Org. Chem.*, **26**, 2277 (1961); P. T. Lansbury and R. Thedford, *ibid.*, **27**, 2383 (1962).

(3) F. Bohlmann, *Chem. Ber.*, **85**, 390 (1952).

(4) (a) R. H. Abeles, R. F. Hutton and F. H. Westheimer, *J. Am. Chem. Soc.*, **79**, 712 (1957); (b) R. H. Abeles and F. H. Westheimer, *ibid.*, **80**, 5459 (1958); (c) E. A. Braude, J. Hannah and R. Linstead, *J. Chem. Soc.*, 3249, 3257, 3268 (1960).

(5) J. K. Ruff, *J. Am. Chem. Soc.*, **83**, 2835 (1961). Reaction of excess dimethylamine with LAH in ether gave $\text{LiAl}(\text{N}(\text{CH}_3)_2)_4$.

(6) On the basis of electronegativities, the Al-N bond has *ca.* six times as much ionic character as the C-N bond.

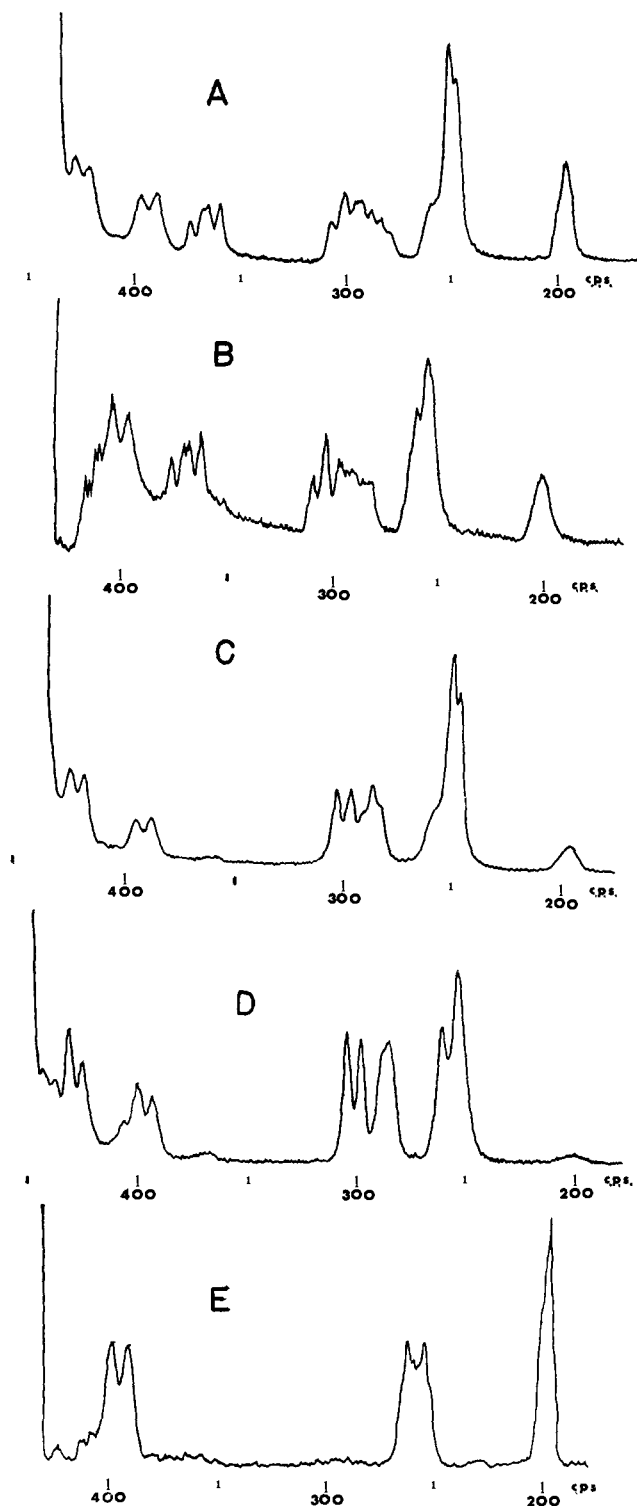
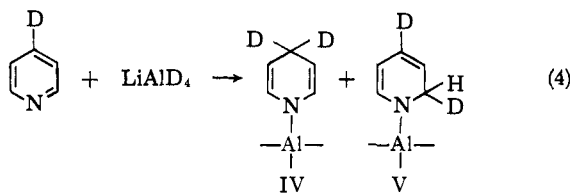


Fig. 1.—Nuclear magnetic resonance spectra of I prepared from: A, pyridine and LiAlH_4 ; B, pyridine and LiAlD_4 ; C, pyridine-4- d_1 and LiAlH_4 ; D, pyridine-4- d_1 and LiAlD_4 ; all at room temperature; and E, pyridine and LiAlH_4 prepared at 60° . pyridine-4- d_1 and LiAlD_4 , in which case species IV and V would be formed.



With IV and V present, any benzhydrol- α -H would necessarily come from V. Infrared analysis of the reduction product in this experiment indicated 48% α -H, whereas 77% would be predicted for V only. This value corresponds to 62% of groups with structure V and agrees nicely with the first experiment dealing with 1,4-dihydropyridyl content. In view of the experimental error, however, one can conclude no more than that the observed 1,2- to 1,4- ratio in I prepared at room temperature is close to the statistical one (1:2), which is quite reasonable for attack by a powerful nucleophile in a polar medium.¹⁵ Another source of discrepancy is the distinct possibility that the reactivity of the 2-methylene and 4-methylene groups as hydride donor centers differs (due to steric effects, etc.) in spite of similar k_H/k_D . Furthermore, the 1,2- to 1,4-ratio is sensitive to temperature (see below) which is a difficulty-controllable variable in various preparations of I. One reason for this is the varying particle size of the LAH, which obviously controls the rate of reaction and hence the degree of exothermicity. Finally, isotopic impurities in the deuterated compounds used is an unavoidable source of small errors.

A more direct method for investigating the 1,2- to 1,4-ratio in I is nuclear magnetic resonance (n.m.r.) spectroscopy. The chemical shifts of the 2- and 4-methylene protons would be expected to be different and at higher field than the vinyl proton signals, which in turn would appear at higher field than pyridine itself, allowing one to make measurements of I in pyridine solution as it forms, as well as on the crystalline salt. However, in view of the complex n.m.r. spectra shown by N-phenyl-1,2-dihydropyridine and N-phenyl-1,4-dihydropyridine,^{11b} we anticipated that compound I would show a very complicated n.m.r. spectrum with extensive spin-spin coupling and this was indeed the case. The 60-Mc. spectra of I and several specifically deuterated analogs are shown in Fig. 1.

As can be seen, several of the resonance peaks are broad multiplets so that there is some uncertainty in the exact position of the center of the peak. Table III give the chemical shifts (c.p.s. from internal tetramethylsilane in pyridine solvent) of the various protons present in I. The appearance of the various signals can be followed with time after LAH and pyridine are initially mixed and the solution immediately transferred to the n.m.r. sample tube. Moreover, the reduction of benzophenone can be observed by n.m.r., which reveals little rate difference in reduction by 2- and 4-methylene groups. Crystalline I gives essentially the same n.m.r. spectrum as aged solutions.

The above assignments of chemical shifts are in good agreement with previous n.m.r. studies by Saunders^{11b} and Kosower,^{11c} on the N-phenyl-1,2- and 1,4-dihydropyridines^{11b} and 1,4,4-trimethyl-1,4-dihydropyridine,^{11b} respectively, and are further confirmed by examining deuterated samples of I (spectra B, C and D). Spectrum B, obtained with LiAlD_4 and $\text{C}_5\text{H}_5\text{N}$, shows decreased intensities for the 200 and 250 c.p.s. peaks, relative to the vinyl proton signals, since the 2- and 4-methylene groups present are now half deuterated. Since the decrease in intensity of the 250 c.p.s. multiplet (2-methylene) is substantially less than the 200 c.p.s. peak (4-methylene), the former must also arise from other protons, namely, the 3- and 5-

(15) The great selectivity of organolithium reagents for α -attack on pyridines may well be due to the highly covalent character of organolithium compounds in ether which results in close proximity of the carbanionoid portion of the reagent to the α -position when lithium initially becomes coordinated to the ring nitrogen. This factor has also been used to explain metalation of aromatic rings *ortho* to a basic substituent.

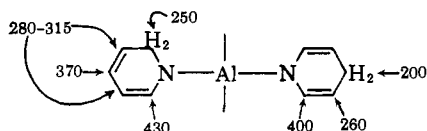
TABLE III

CHEMICAL SHIFTS OF PROTONS IN LITHIUM TETRAKIS-(N-DIHYDROPYRIDYL)-ALUMINATE (I)

| Peak, c.p.s. | Assignment |
|----------------------------------|---|
| 200 | 4-Methylene |
| 250-260 | 2-Methylene plus 3- and 5-vinyl protons in 1,4-dihydropyridyl |
| 280-315 | 3- and 5-vinyl protons in 1,2-dihydropyridyl |
| 370 (quartet, due to ABC system) | 4-Vinyl proton |
| 400 (doublet, $J \sim 7$ c.p.s.) | 2- and 6-vinyl protons in 1,4-dihydropyridyl |
| 430 ^a | 6-Vinyl proton in 1,2-dihydropyridyl |

^a This peak was observable only in pyridine-4-*d*₁ or pyridine-*d*₅ solution.

protons in the 1,4-dihydropyridyl groups.¹⁶ This is expected from Saunders' results^{11b} and additionally verified below. The assignment of the 200 c.p.s. peak to 4-methylene is further proved by examining spectrum C, which shows I prepared from LAH and pyridine-4-*d*₁. It should be noted that the 200 c.p.s. peak is reduced in intensity to about half and that the 250 c.p.s. multiplet is unchanged. In addition, the 370 c.p.s. signal has disappeared, as expected, since there is now no 4-vinyl proton. Spectrum D, obtained from LiAlD₄ and pyridine-4-*d*₁, shows no 4-CH₂ signal and no 4-vinyl proton signal as predicted. From the above firmly assigned peaks and by examination of relative areas under peaks, it is possible to assign the remaining signals as indicated in Table III and summarized in the partial structural formula



The 430 c.p.s. multiplet is usually hidden by pyridine absorption, but is partly observable in pyridine-4-*d*₁ and pyridine-*d*₅ solvent. In the latter solvent, the 6-vinyl proton signal appears as a shoulder at the high field side of the intense signal arising from the β - and γ -protons of pyridine (of solvation in crystalline I). Integration of the α -proton signal of pyridine and comparison of the area with the above peak gives a ratio greater than 2:3 as demanded for pyridine itself. The excess area of the latter peak coincides with that of the 4-vinyl proton multiplet at 370 c.p.s., thus confirming the assignment of the 430 c.p.s. absorption.

We have been able to prepare samples of I containing almost entirely 1,4-dihydropyridine groups, by aging LAH in pyridine at 60° rather than 0-25° as usual. This solution (spectrum E) shows only three groups of signals, at 200, 260 (relative area 1:1.1 indicating *ca.* 10% of 2-methylene in the 260 c.p.s. peak) and at 400 c.p.s. Further investigation of the effect of temperature on the structure of I revealed that this variable exerts a profound effect on the 1,2- to 1,4-ratio, as shown in Table IV.

TABLE IV

EFFECT OF TEMPERATURE OF AGING ON 1,2- TO 1,4-DIHYDROPYRIDYL RATIO IN I

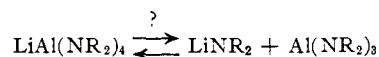
| Temp., °C. | -30 | 0 | 25 | 60 |
|------------|-----|----|----|----|
| % 1,4- | 27 | 31 | 51 | 90 |
| % 1,2- | 73 | 69 | 49 | 10 |

(16) This portion is actually on the downfield side of the multiplet, at *ca.* 260 c.p.s.

The above results were obtained by taking the ratio of the integrated areas of the 200 c.p.s. peak (1,4-content) to the entire 250-260 c.p.s. multiplet (total dihydropyridyl content) or in several cases by comparing the areas of the 200 c.p.s. peak with the 4-vinyl proton signal (which corresponds to 1,2-dihydropyridyl content). The above ratios reported in Table IV are in good qualitative agreement with the previously mentioned infrared results obtained from samples of I prepared at 0-25° without rigorous temperature control. Additional evidence that the 1,4-dihydro isomer is the thermodynamically more stable will be presented in a subsequent paper.¹⁷

Finally, we were able to confirm by n.m.r. that I does contain *four* dihydropyridyl groups, in accord with previously suggestive infrared results mentioned above, by using *t*-butylbenzene in known concentration as an internal standard and integrating the entire 250-260 c.p.s. multiplet. Comparison of peak areas gave 3.5 dihydropyridyl groups per aluminum.¹⁸

An additional point concerning I is the possibility of its dissociation into a lithium amide and a trivalent aluminum amide, especially in solution.



Crystalline I does not melt without decomposition and is insoluble in non-polar solvents such as benzene, ether and petroleum ether, but is soluble in acetonitrile as well as pyridine. These observations favor the tetrasubstituted aluminate structure, since compounds of the type Al(NR₂)₃ generally have low melting points and are soluble in non-polar media.⁵

We now turn our attention to the reducing action of I on organic compounds. Initially, the reactivity of monofunctional compounds with I was studied by examining substrates individually, then in pairs by means of competition experiments. Table V summarizes the results of reactions of various ketones and carboxylic acids and esters with excess I at room temperature. An excess of reducing agent was used for comparing the reactivity of various functional groups since it has been found that the first equivalent of hydride is transferred more rapidly than the second when *excess benzophenone* was being treated with I; furthermore, the third and fourth hydrogens reacted only slowly. It can be seen that diaryl ketones are much more reactive than the other functional groups studied. In addition to the reactions of I with carbonyl compounds, reduction of nitro groups has been observed. Nitrobenzene gave azoxybenzene as the major product (*ca.* 75%) when treated with I, in the mole ratio 2:1, for 5 hr.¹⁹ The effect of varying temperature and reactant ratios on the yield and reaction course is being further investigated. An exploratory reaction of styrene oxide with excess I for 4 hr. resulted in a 50% yield of α - and β -phenylethanols in the ratio 60:40.²⁰ The slow reduction of the above epoxide suggests that such a group might survive in selective reductions by I of more reactive groups in polyfunctional compounds.

From the above results, it appeared that certain ketoacids and ketoesters could be selectively reduced to lactones, rather than diols, by cyclization of the hydroxy acids or esters initially formed.

(17) J. O. Peterson, unpublished results.

(18) This is significantly more than three, although somewhat less than theoretical; however, it is expected that the observed value might be less than four since mere traces of moisture, etc., would lessen the value appreciably by consuming I.

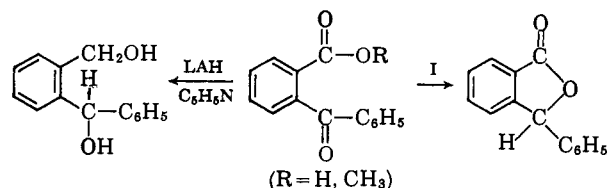
(19) R. E. MacLeay, unpublished results.

(20) L. W. Trevo, and W. G. Brown, *J. Am. Chem. Soc.*, **71**, 1675 (1949), report 75% α -phenylethanol from reduction of styrene oxide with LAH in ether.

TABLE V
REDUCTION OF CARBONYL COMPOUNDS BY LITHIUM TETRAKIS-(N-DIHYDROPYRIDYL)-ALUMINATE (I)

| Compound | Mole ratio I/comp. | Time | Product (% yield) ^a |
|--|--------------------|--------|---|
| A. Diaryl ketones | | | |
| Benzophenone | 1.25 | 3 hr. | Benzhydrol (<i>ca.</i> 100; I. R.) |
| Benzophenone | 1.25 | 5 min. | Benzhydrol (92-95; G. C.) |
| 9-Fluorenone | 1.25 | 5 min. | 9-Fluorenone (<i>ca.</i> 100; I. R.) |
| 1,5-Dimethyl-7(12H)-pleiadone | 1.25 | 20 hr. | Pleiadone (<i>ca.</i> 100; I. R.) |
| 4,4'-Dichlorobenzophenone | 1.25 | 3 hr. | 4,4'-Dichlorobenzhydrol (<i>ca.</i> 100; I. R.) |
| 4,4'-Dimethylbenzophenone | 1.25 | 3 hr. | 4,4'-Dimethylbenzhydrol (<i>ca.</i> 100; I. R.) |
| B. Aryl alkyl ketones | | | |
| Acetophenone | 1.25 | 12 hr. | 1-Phenylethanol (32; G. C.) |
| 3-Methoxyacetophenone | 1.25 | 12 hr. | 1- <i>m</i> -Anisylethanol (70; G. C.) |
| 4-Methoxyacetophenone | 1.25 | 12 hr. | 1- <i>p</i> -Anisylethanol (29; G. C.) |
| 1-Indanone | 2.5 | 6 hr. | 1-Indanol (16; G. C.) |
| 1-Tetralone | 2.5 | 6 hr. | 1-Tetralol (3; G. C.) |
| 1-Benzuberone | 2.5 | 6 hr. | 1-Benzuberol (14; G. C.) |
| Benzpinacolone | 1.9 | 40 hr. | Triphenylmethane (77) |
| α,α,α -Trifluoroacetophenone | 2 | 2 hr. | Trifluoromethylphenylcarbinol (83; G. C.) |
| C. Dialkyl ketones | | | |
| 2-Octanone | 1.25 | 12 hr. | 2-Octanol (69; G. C.) |
| Methyl benzyl ketone | 1.25 | 12 hr. | Methylbenzylcarbinol (58; G. C.) |
| 2-Methylcyclopentanone | 20 | 5 days | 2-Methylcyclopentanol (8% <i>trans</i> , 27% <i>cis</i> ; G. C.) |
| Camphor | 7 | 5 days | 98% recovd. ketone |
| 2,4,4-Trimethylcyclopentanone | 23 | 5 days | 2,4,4-Trimethylcyclopentanol (20% <i>trans</i> , 5% <i>cis</i> ; G. C.) |
| 4- <i>t</i> -Butylcyclohexanone | 24 | 5 days | 4- <i>t</i> -Butylcyclohexanol (37% <i>trans</i> , 8% <i>cis</i> ; G. C.) |
| D. Carboxylic acids and esters | | | |
| 1-Naphthoic acid | 1 | 6 hr. | No reacn. (I. R.) |
| Stearic acid | 2.6 | 18 hr. | No reacn. (I. R.) |
| Methyl 1-naphthoate | 1.25 | 20 hr. | No reacn. (I. R.), 75% recovery |
| <i>n</i> -Butyl stearate | 2.6 | 18 hr. | No reacn. (I. R.) |
| <i>dl</i> - α,α' -Dimethylhydrobenzoin carbonate | 1.3 | 44 hr. | No reacn. (I. R.) |

^a In cases where product isolation was not carried out, the analysis was done by infrared spectroscopy (I. R.) or gas chromatography (G. C.).

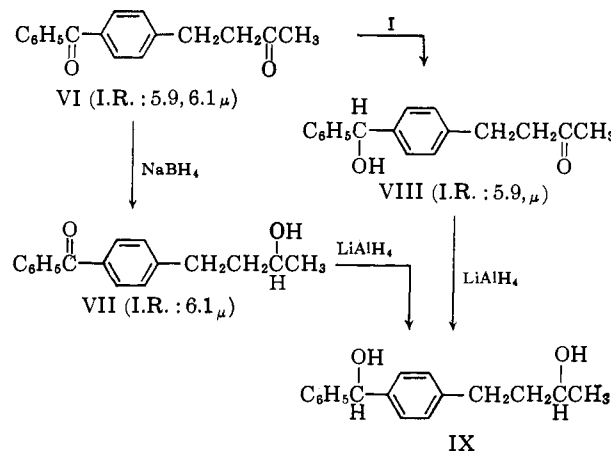


The above-anticipated selectivity was dramatically illustrated with *o*-benzoylbenzoic acid or the methyl ester. Excess LAH added to the substrate in pyridine gave predominant reduction to the diol within 15 min. (by infrared), whereas overnight exposure to excess I afforded 3-phenylphthalide in excellent yield (*e.g.*, 93% from the ketoacid). Other ketoacids (or esters) showing the above-typified selective reductions by I were *o*- α -naphthoylbenzoic acid and 8-benzoyl-1-naphthoic acid.

The unique reactivity of various types of ketones toward I is most interesting²¹ and was further explored in several selected diketones in order to demonstrate intramolecular selectivity, as well as that observed in competition experiments (*e.g.*, 1-tetralone *vs.* benzophenone and 2-octanone *vs.* benzophenone, in which experiments the latter was almost completely reduced in each case without appreciable consumption of the former). Accordingly, 4-phenyl-2-butanone was benzoylated with aluminum chloride catalyst, yielding 4-(*p*-benzoylphenyl)-2-butanone (VI) and the diketone, which possesses both diaryl and dialkyl carbonyl groups, reduced by I and by sodium borohydride.

(21) Our attention was initially drawn to this phenomenon when we observed the sluggishness of 4-*t*-butylcyclohexanone toward I during prolonged periods (3-5 days) when attempting to study the stereochemical aspects of this reduction.

As expected,²² the latter reagent reduced VI selectively at the *dialkyl* carbonyl group, giving a 46% yield of 4-(*p*-benzoylphenyl)-2-butanol (VII) as well as a 54% yield of the diol IX resulting from complete reduction. Conversely, the dihydropyridine reagent reacted with VI to give a 56% yield of the isomeric ketol VIII together with some diol. The formation of diol in these two selective reductions could undoubtedly be minimized by further adjustment of conditions, *e.g.*, reduced reaction times and/or less reducing agent.



The product mixtures were separated by gradient elution chromatography and the two oily ketols characterized by infrared spectroscopy, each showing only a single characteristic carbonyl band (see above), and

(22) H. C. Brown, O. H. Wheeler and K. Ichikawa, *Tetrahedron*, **1**, 214 (1957); H. C. Brown and K. Ichikawa, *J. Am. Chem. Soc.*, **84**, 373 (1962).

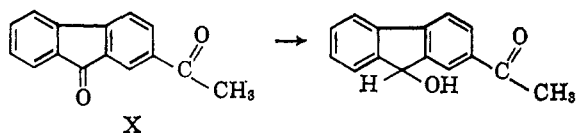
further reduction to a common diol (mixture of racemates) which showed no intense ultraviolet absorption and analyzed correctly. Further confirmation for the structures of VII and VIII comes from the crystalline 2,4-dinitrophenylhydrazones, which not only gave satisfactory elemental analyses but also characteristic absorption maxima in the visible region which were in line with those of suitable model compounds, as shown in Table VI. The synthetic utility of I in reducing diketones such as 4-(*p*-benzoylphenyl)-2-butanone is attested to by the fact that a more conventional multi-step conversion to ketol VIII (by selective ketalization of the diketone, followed by reduction of the diaryl carbonyl group and subsequent ketal hydrolysis) failed to provide the desired product in reasonable yield or purity.

TABLE VI
VISIBLE ABSORPTION SPECTRA OF
2,4-DINITROPHENYLHYDRAZONES

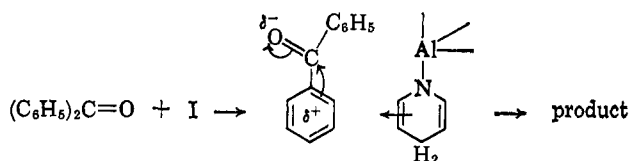
| Compound | λ_{\max} , m μ | ϵ |
|----------------------|---------------------------------------|------------|
| VII-2,4-DNPH | 381 (EtOH) | 28,600 |
| 4-Methylbenzophenone | | |
| 2,4-DNPH | 390 ^a (CHCl ₃) | 28,000 |
| VIII-2,4-DNPH | 359 (EtOH) | 22,400 |
| 2-Butanone 2,4-DNPH | 362 ^b (EtOH) | 23,000 |

^a C. D. Johnson, *J. Am. Chem. Soc.*, **75**, 2720 (1953). ^b E. A. Braude and E. R. H. Jones, *J. Chem. Soc.*, 735 (1942).

A second diketone which underwent selective reduction by I is 2-acetyl-9-fluorenone (X). In view of the fact that fluorenone undergoes sodium borohydride reduction faster than benzophenone²³ it is understandable that no selectivity was observed in reducing X, as judged by the relative intensities of the two ketone carbonyl bands (at 1700 and 1650 cm.⁻¹) in reactant and crude product. With I, however, it was anticipated that the acetyl group should be reduced only slowly and this was confirmed by the isolation of a 40% yield of 2-acetyl-9-fluorenol (plus 28% recovered diketone and ca. 15% of the diol).



The unusual order of reactivity of various types of ketones toward I is of theoretical as well as synthetic interest. It is possible that benzophenones react by an entirely different mechanism than the other ketones, since no other addition reactions of diaryl ketones occur with such relative ease. One possibility is initial formation of a charge-transfer complex^{11c} followed by intramolecular hydride transfer within the complex.



The aryl group that is unconjugated with the carbonyl, due to out-of-plane bending²⁴ exerts a -I effect which facilitates hydride transfer. α, α, α -Trifluoroacetophenone, as expected, underwent reduction almost as rapidly as benzophenone (81% yield of carbinol after 2 hr.); about 5% of an inseparable contaminant in the ketone may have prevented an even faster reduction. On the other hand, in acetophenones π -complexing is

(23) R. B. Bayer, Ph.D. Dissertation, Washington State University.

(24) R. N. Jones, *J. Am. Chem. Soc.*, **67**, 2141 (1945).

also possible, but the methyl group has a +I effect on the carbonyl group, which decreases its electrophilicity and lowers the rate of nucleophilic attack. It is anticipated that studies of substituent effects in a series of benzophenones²⁵ and acetophenones will provide information on the mechanisms of these reductions. The determination of Hammett ρ -values for these two series is presently underway in our laboratory, as well as further studies of selective reductions.

In summary, it is now possible to use LAH and pyridine either as a potent, but indiscriminant, reducing system, by direct addition of LAH to the substrate in pyridine, or as a mild, selective reagent, by prior formation of an anionic dihydropyridine derivative. These techniques will hopefully further enhance the already tremendous versatility of the complex metal hydrides and their derivatives.²⁶

Experimental²⁷

Reagents.—Lithium aluminum hydride and deuteride were obtained from Metal Hydrides, Inc., the former being purified by evaporation of filtered ether solutions. Reagent-grade pyridine was distilled from barium oxide and stored over it prior to use. Deuterated pyridines were obtained from Merck, Sharp and Dohme, Ltd., Montreal, Can., and had better than 98% isotopic purity. Most of the compounds used in reduction studies were obtained from commercial sources or prepared by standard synthetic methods. The syntheses of new compounds are described below.

Preparation of I and General Procedure for Reductions.—Solutions of I for structure and reduction studies were generally prepared on a small scale, since addition of large quantities of LAH (> 1 g.) to pyridine may lead to highly exothermic reactions. Typically, 0.5 g. (0.013 mole) of LAH was gradually added to 50 ml. of anhydrous pyridine in an ice-cooled 60-ml. serum bottle equipped with a rubber cap. After the initial reaction, the cap was tightened and the pale orange solution (0.26 M in LAH initially) aged as desired. Generally, the solutions were kept at 20–25° except in those cases where the effect of temperature on the structure of I was studied, in which case samples were aged at 60°, 25°, 0° and -30°. Aliquots of the pyridine solution of I were removed as desired by means of a hypodermic syringe and transferred to a reaction vessel containing the substrate to be reduced in pyridine, or to n.m.r. sample tubes, etc.

In cases where crystalline I was desired, 0.5 M solutions were prepared in a nitrogen-flushed drybox and filtered in it, through a sintered glass funnel to remove insoluble impurities present in commercial LAH. On standing, chunky, pale yellow crystals of I separated; these were filtered in the drybox and subsequently dried *in vacuo* at room temperature. The vacuum-dried crystals had a pyridine odor and were extremely hygroscopic in air, making further manipulations possible only in a drybox. The crystals decomposed without melting when heated.

Anal. Calcd. for C₂₀H₂₄N₄LiAl: C, 67.79; H, 6.83; N, 15.81; residue (as metal oxides), 18.60. Found: C, 61.19; H, 6.60; N, 8.64; residue, 19.08.

Reductions of 1–2 mmoles of substrate, using crystals of I redissolved in pyridine or, more generally, directly-aged solutions, usually involved equimolar or greater amounts of I in order to ensure complete reaction where one occurred and to demonstrate clearly the inertness of those groups that are unaffected by I (e.g., carboxylic acids and esters). The reaction mixtures were hydrolyzed by addition of methanol, then poured into a mixture of ether and 5% hydrochloric acid. The ether extract was further washed with 5% hydrochloric acid, sodium chloride solution, 5% sodium bicarbonate and then dried over sodium sulfate. Evaporation of the dried ether solution provided the crude product, which was either recrystallized or directly analyzed by infrared spectroscopy and/or gas-liquid partition chromatography (see Table V for individual experiments).

(25) Competitive reductions of a number of substituted diaryl ketones with I at room temperature have established the following order of relative reactivities: 4,4-dichlorobenzophenone > fluorenone > 2,4-dichlorobenzophenone > 4-chlorobenzophenone > benzophenone > 4-methylbenzophenone > 4,4'-dimethylbenzophenone (R. E. MacLeay, unpublished results).

(26) H. C. Brown, *J. Chem. Educ.*, **38**, 173 (1961).

(27) Melting points and boiling points are uncorrected. Analyses were performed by Dr. Alfred Bernhardt, Mulheim, Germany. Infrared spectra were taken on a Perkin-Elmer model 21 or Beckman model IR-5 spectrophotometer, using Nujol mulls or neat liquids between salt plates. Nuclear magnetic resonance spectra were obtained with a Varian A-60 instrument, using pyridine as solvent and tetramethylsilane as internal standard. Gas-liquid partition chromatograms were obtained using an F and M model 300 linear programmed temperature chromatograph.

Samples of I with deuterium labeling were prepared as above, except on a smaller scale. The ratio of benzhydrol to benzhydrol- α -D resulting from reduction of benzophenone by deuterated I (Table I) was determined by infrared spectroscopy, using the C-H and C-D stretching bands at 2870 and 2120 cm^{-1} , respectively, for determining H/D content *via* the base line method. Examination of synthetic mixtures of pure benzhydrol and benzhydrol α -D provided linear calibration plots for both peaks. A 0.5-mm. cell was used with carbon tetrachloride as solvent.

Competitive Reductions of Ketones by I. a. **Benzophenone vs. 1-Tetralone.**—A pyridine solution containing equimolar amounts of the above ketones (2 mmoles each) was allowed to react with excess reducing agent (5 mmoles) for 3.5 hr., then worked up. The crude product (ν_{max} 3400 cm^{-1} , O-H; 1675 cm^{-1} , 1-tetralone carbonyl) contained at best only a trace of benzophenone as indicated by lack of infrared absorption at 1650 cm^{-1} . Treatment with 2,4-dinitrophenylhydrazine reagent gave a 95% yield of 1-tetralone 2,4-dinitrophenylhydrazone, m.p. 258–260°, which checked with an authentic sample.

b. **Benzophenone vs. 2-Octanone.**—When an equimolar mixture of the two ketones (2 mmoles each) was allowed to react with excess I (5 mmoles) in pyridine for 1 hr., then hydrolyzed and worked up, the crude product showed nearly complete disappearance of the 1650 cm^{-1} band of benzophenone but the 1700 cm^{-1} band of 2-octanone was still quite intense. Gas chromatography on a Tide column gave the composition (mole %): 42% 2-octanone, 8% 2-octanol, 3% benzophenone and 47% benzhydrol.

Selective Reduction of *o*-(α -Naphthoyl)-benzoic Acid by I.—To a solution of 0.80 g. (2.9 mmoles) of *o*-(α -naphthoyl)-benzoic acid in 5 ml. of pyridine was added (syringe) 18 ml. of a 0.26 M solution of I in pyridine (4.7 mmoles). The initial exothermic reaction resulted in a lightening of the orange color; after 38 hr. the mixture was worked up as usual except that the acid hydrolysis mixture was warmed for 15 min. on a steam-bath before the product was extracted into ether (to complete lactonization of any hydroxyacid remaining). The crude oily product (0.57 g., 76% yield) showed a strong infrared lactone carbonyl band at 1752 cm^{-1} and no absorption due to starting material (1655 and 1672 cm^{-1}). Crystallization from 80% methanol gave pure 3- α -naphthylphthalide, m.p. 135–137° (reported²⁸ 137–138°), whose infrared spectrum was unchanged from that of the crude product.

Using the same ratios of reactants and conditions as above, methyl *o*-(α -naphthoyl)-benzoate gave a 78% yield of 3- α -naphthylphthalide.

Treatment of 0.45 g. (1.6 mmoles) of the above ketoacid with excess sodium borohydride (2.6 mmoles) in methanol for 4 hr., followed by hydrolysis and work-up, resulted in a nearly quantitative recovery of starting material, whose infrared spectrum was superimposable on that of the ketoacid.

A similar scale reaction with excess lithium aluminum hydride in pyridine for 15 min. gave complete reduction of both functional groups to the diol, as indicated by the infrared spectrum of the crude product in chloroform solution, which showed no carbonyl absorption but strong O-H absorption at 2.8–3.0 μ . Recrystallization from aqueous methanol (Norit) gave colorless crystals, m.p. 131–133°.

Anal. Calcd. for $\text{C}_{18}\text{H}_{16}\text{O}_2$: C, 81.80; H, 6.09. Found: C, 81.55; H, 6.18.

Selective Reduction of *o*-Benzoylbenzoic Acid.—Treatment of 1 g. (4.5 mmoles) of *o*-benzoylbenzoic acid with 5.0 mmoles of I in pyridine for 4 hr., followed by work-up, gave a 93% yield of 3-phenylphthalide, m.p. 115–116.5° (reported²⁹ 116–117°), ν_{max} 1740 cm^{-1} (in Nujol).

Starting from methyl *o*-benzoylbenzoate, the lactone was obtained in 62% yield.

When *o*-benzoylbenzoic acid was reduced with LAH in pyridine, the major product was the diol, judging from infrared examination.

Preparation of 4-(*p*-Benzoylphenyl)-2-butanone (VI).—To a stirred solution of 50 g. (0.375 mole) of aluminum chloride in 250 ml. of carbon disulfide was added 16.3 ml. (0.14 mole) of benzoyl chloride and 22.9 ml. (0.15 mole) of benzylacetone. During the addition and for 1 hr. after, the reaction mixture was kept at 0°, then allowed to warm to room temperature and stand overnight. The dark brown solution was hydrolyzed by pouring onto a mixture of ice and concentrated hydrochloric acid, then worked up in the usual manner. Crude VI was purified by distillation under reduced pressure, b.p. 185–200° (2 mm.), yielding a colorless oil which solidified on standing. Recrystallization from benzene-petroleum ether gave 16.4 g. (26%) of pure diketone as colorless needles, m.p. 35–37°. The infrared spectrum showed two distinct carbonyl bands at 1700 and 1650 cm^{-1} (dialkyl and

diaryl carbonyl, respectively) and the ultraviolet spectrum showed $\lambda_{\text{max}}^{\text{EtOH}}$ 259, $\log \epsilon$ 4.3.

Anal. Calcd. for $\text{C}_{17}\text{H}_{16}\text{O}_2$: C, 80.93; H, 6.39. Found: C, 80.64; H, 6.39.

Reaction of VI with excess hydroxylamine hydrochloride in ethanol led to the isolation of the dioxime, m.p. 143–144°, whose infrared spectrum showed strong O-H absorption at 3200 cm^{-1} and no carbonyl bands.

Anal. Calcd. for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_2$: N, 8.64. Found: N, 9.09.

A half-gram sample of VI was oxidized with hot alkaline permanganate solution, yielding crude *p*-benzoylbenzoic acid, m.p. 190–194° (reported³⁰ 194°) in 78% yield as the only isolable product.

Selective Reduction of 4-(*p*-Benzoylphenyl)-2-butanone (VI). a. **With Complex I.**—A solution of 32.5 mmoles of I in pyridine (125 ml.) was added to 1.25 g. (5 mmoles) of VI in 10 ml. of pyridine. After 3 hr., the reaction mixture was poured onto an ice-dilute hydrochloric acid mixture. Work-up provided 1.11 g. of brownish oil whose infrared spectrum (neat) showed a strong dialkyl carbonyl band at 1700 cm^{-1} and only weak diaryl carbonyl absorption at 1650 cm^{-1} . A portion of this material (0.93 g.) was chromatographed on silica gel, using a gradient elution system with petroleum ether (b.p. 30–60°), benzene and ether in that order. Approximately 50 cuts were taken. The first compound eluted was starting material VI (8% recovery), followed by a 56% yield (0.515 g.) of ketol VIII, which showed only a 1700 cm^{-1} carbonyl band in the infrared and no strong ultraviolet absorption. The third component eluted was the diol (0.34 g., 36% yield).

The oily ketol VIII was further characterized by conversion to a crystalline orange 2,4-dinitrophenylhydrazone, m.p. 88–91° (from ethanol), $\lambda_{\text{max}}^{\text{EtOH}}$ 359 μ , $\log \epsilon$ 4.35.

Anal. Calcd. for $\text{C}_{23}\text{H}_{22}\text{N}_4\text{O}_5$: C, 63.59; H, 5.10; N, 12.90. Found: C, 64.21; H, 5.22; N, 13.06.

The above diol IX was identical (by infrared) with that prepared by LAH reduction of VI in 98% yield as a colorless oil (mixture of racemates).

Anal. Calcd. for $\text{C}_{17}\text{H}_{20}\text{O}_2$: C, 79.65; H, 7.86. Found: C, 79.66; H, 7.73.

Treatment of IX with 3,5-dinitrobenzoyl chloride in pyridine afforded a crystalline bis-3,5-dinitrobenzoate, m.p. 70–74°.

Anal. Calcd. for $\text{C}_{31}\text{H}_{24}\text{N}_4\text{O}_{12}$: C, 57.77; H, 3.75. Found: C, 58.18; H, 3.91.

b. **With Sodium Borohydride.**—Equimolar amounts (5 mmoles) of VI (1.26 g.) and sodium borohydride (0.19 g.) in absolute ethanol (100 ml.) were kept for 1 hr. at room temperature, then hydrolyzed with 10% hydrochloric acid and worked up. The crude oil (1.03 g.) was chromatographed over silica gel as above, yielding 46% (0.473 g.) of ketol VII and 54% of diol IX. Compound VII showed O-H absorption in the infrared at 2.7–3.0 μ and a single carbonyl band at 1650 cm^{-1} . Treatment of VII with 2,4-dinitrophenylhydrazine reagent gave a reddish orange derivative, m.p. 155–157° (from ethanol-water), $\lambda_{\text{max}}^{\text{EtOH}}$ 381 μ , $\log \epsilon$ 4.46.

Anal. Calcd. for $\text{C}_{23}\text{H}_{22}\text{N}_4\text{O}_5$: C, 63.59; H, 5.10; N, 12.90. Found: C, 64.01; H, 5.18; N, 12.80.

Selective Reduction of 2-Acetyl-9-fluorenone (X).—2-Acetyl-9-fluorenone³¹ (1.1 g., 5 mmoles) dissolved in ca. 20 ml. of pyridine was treated with 50 ml. of I (13 mmoles) and allowed to react for 1 hr. From work-up, 1.08 g. of brownish yellow oil was obtained whose infrared spectrum showed O-H (3400 cm^{-1}) and a substantial decrease in the intensity of the 9-carbonyl group (1700 cm^{-1}) with respect to that of the 2-acetyl group (1650 cm^{-1}). Gradient elution chromatography over alumina, using petroleum ether-ether solvent, gave 28% of recovered X, 40% of 2-acetyl-9-fluorenone (XI) and 15% of the diol. Recrystallization of XI gave colorless crystals (from benzene-petroleum ether), m.p. 146–147°, showing a single carbonyl band at 1650 cm^{-1} , as in 2-acetylfluorene.

Anal. Calcd. for $\text{C}_{15}\text{H}_{12}\text{O}_2$: C, 80.34; H, 5.39. Found: C, 80.19; H, 5.37.

Several exploratory reactions of X with sodium borohydride in ethanol failed to yield any selective reduction of either carbonyl group.

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