AROMATIC SUBSTITUTION

PART V.[1] THE MECHANISM OF THE REACTION OF PHENYLLITHIUM WITH PYRIDINES. DEUTERIUM ISOTOPE EFFECT STUDIES

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ABSTRACT

The ratios of isomers formed in the reaction of 3-alkylpyridines with phenyllithium under various conditions appear to be invariant within the limits of experimental error. A number of experiments, including the reaction of phenyllithium with 3-picoline-2d and with an excess of a mixture of pyridine and pyridine-2d, are described which establish that the hydride ion elimination stage in these nucleophilic aromatic substitutions is not important in determining the observed orientation and that the addition stage is either virtually irreversible or that the equilibrium lies far on the product side and is not rapidly reversible. A convenient new procedure is described for working up the reaction mixtures.

In previous parts of this series (1, 2) the reaction of 3-substituted pyridines with phenyllithium has been studied, particular emphasis being placed upon the determination of the orientation of the entering phenyl group and the isomer ratios. It was shown that in the case of most 3-substituents the main product formed was the 2,3-disubstituted pyridine derivative, the 2,5-isomer usually being formed in lesser amounts. In no case was any attack at C_4 of the pyridine ring observed. A number of possible explanations for the observed orientation were considered (1). Among other possibilities it was pointed out that if the second stage in these reactions, the elimination of hydride ion, is rate-determining, and *if it is assumed that the addition step is rapidly reversible* the results might be explained as follows (3-picoline is taken as an example):

(i)
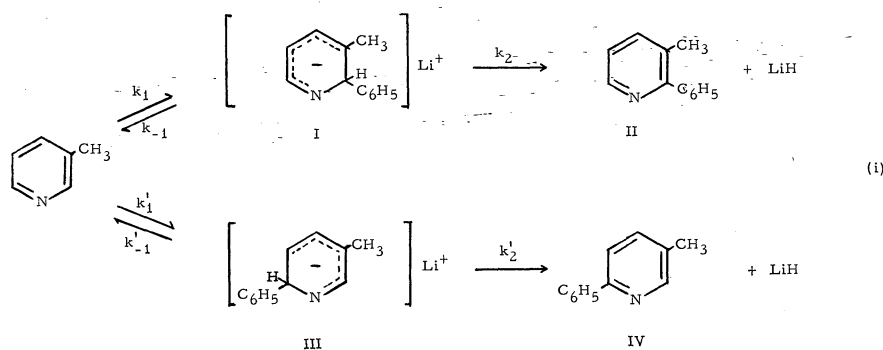
The aromatization step in (i) probably involves the abstraction by the lithium cation of the hydrogen atom with its bonding pair of electrons. The energy of activation for this step would probably be lowered more by an electron-repelling ortho-methyl than by a para-methyl group. This effect might well be greater than the opposing steric effect favoring hydride expulsion from III over that from I.* If this is so, k_2 would be greater

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[1]*Part IV: R. A. Abramovitch, W. A. Hymers, J. B. Rajan, and R. Wilson. Tetrahedron Letters, 1507 (1963).*
If the transition state resembles product there would be appreciable 1,2-alkyl:phenyl repulsion in the case of $I \rightarrow II$.

than k_2' and more II would be formed than IV even though K_1' were greater than K_1, provided the addition step is rapidly reversible. It is to be noted that whereas the addition step is exothermic, heat is required to cause the elimination to take place. In addition, the formation of intermediates such as (I) and (III) finds support in the oxidation of the pyridine–phenyllithium adduct with benzophenone (3), when a by-product, probably 4-diphenylhydroxymethyl-2-phenylpyridine (V), is also formed. This presumably arises by the addition of the 2-phenyl-1,2-dihydropyridyllithium intermediate to benzophenone followed by oxidation and a molecular rearrangement (3).

In order to test the above possibility the reactions of phenyllithium with deuterated pyridine and deuterated picoline were examined. Before doing so, however, it was decided to re-examine the ratios of isomers formed in the reaction between phenyllithium and a 3-alkylpyridine when the phenyllithium solution was added to an excess of the 3-alkyl-pyridine (which was, therefore, always present in excess throughout the reaction) instead of the other way around (when phenyllithium was present in excess, at least in the initial stages). In this way, it was hoped to get a better indication if possible of the relative discrimination of the attacking reagent towards C_2 and C_6. The results are summarized in Table I. The reaction mixtures were worked up in the usual way by heating with

TABLE I

Addition of phenyllithium to an excess of 3-R-pyridine

R	Overall yield* of phenyl-3-R-pyridine (%)	Ratio of 2,3- to 2,5-isomer
CH_3	48	94:6
C_2H_5	42	87:13
iso-C_3H_7	32	76:24
H	26.7†	—
CH_3	25.6†	96:4
C_2H_5	13.6†	89:11
CH_3	33.8‡	95:5
C_2H_5	23.4‡	87:13

*Based on phenyllithium.
†In the presence of an excess of lithium bromide.
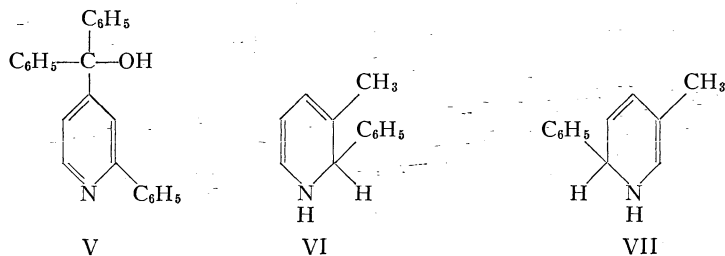‡Using halide-free phenyllithium.

toluene at ca. 110°. The ratios of the 2,3- to the 2,5-phenylalkylpyridines are the same, within experimental error, as those obtained when the addition was carried out in the reverse order (1).

During the course of this work a much more convenient procedure for the working up of the reaction mixture resulting from the addition of an organo-lithium compound to pyridines was developed. After the addition was completed and the mixture had been stirred at room temperature for varying lengths of time dry oxygen was slowly bubbled through the ethereal suspension: oxidation of the dihydropyridyllithium intermediate occurred readily (3) to give the required reaction products and probably lithium hydroxide. The isomer ratios were essentially unchanged, but the overall yields of products are usually somewhat higher—this may well be due to the fact that extensive polymerization of the dihydropyridyllithium intermediate takes place, particularly when it is heated.

The isomer ratio for the addition of phenyllithium to 3-picoline also remained unchanged when the reaction was carried out in dry light petroleum or in dry benzene instead of in ether. When an ethereal solution of the 3-picoline–phenyllithium adduct was stirred at room temperature for various intervals of time (from 6 to 90 hours) before being worked up, again no change in the isomer ratio was observed but the yield of products rose from

20.5 to 42.9%. The reactions with 3-picoline and with 3-ethylpyridine with phenyllithium in ether were also carried out in the presence of an excess of anhydrous lithium bromide. The reactions appeared to proceed more slowly under these conditions (as indicated by the evolution of heat) than when one equivalent of lithium bromide was present (which normally arises from the method of preparation of phenyllithium using bromobenzene and lithium in dry ether), and the overall yields of products were somewhat lower; on the other hand, the 2,3- to 2,5-isomer ratios were unchanged within the limits of accuracy of the experiments ($\pm 2\%$). Finally, the reactions were carried out using halide-free phenyllithium from diphenylmercury and lithium metal (6): once again the isomer ratios remained constant.

In order to test whether the possible reversibility of the addition step had any influence upon the isomer ratios observed, the reaction of phenyllithium with an excess of 3-picoline was interrupted by the addition of water after only a small percentage of the addition had occurred. The 1,2-dihydrophenylpicolines (VI) and (VII) thus formed (4) cannot revert to starting material and, if oxidized, should give the isomeric phenylpicolines in a ratio indicative of the actual orientation in the addition step. Thus, one might then expect that if equations (i) hold and $K_1' > K_1$ (the inductive effect of the methyl group would render attack at C_6 more likely than at C_2) one would get more 2,5- than 2,3-isomer. When the suspension of the dihydropyridines obtained after treatment with water was either oxidized directly with chloranil (5) or extracted with ether and the ethereal extract oxidized and the products analyzed by gas chromatography, the ratio of 3-methyl-2-phenylpyridine to 5-methyl-2-phenylpyridine was still found to be about 94:6. These results would indicate that the addition reactions are virtually irreversible, or that the equilibria as in (i) lie far on the side of the addition products and that equilibration of I and III via starting material is so slow as not to be of importance here.

This has been confirmed in two ways. The importance of the hydride ion elimination step upon the orientation of the products formed was determined by measuring the ratio of isomers formed in the reaction of halide-free phenyllithium with 3-picoline-2d. Since k_H/k_D in hydride ion eliminations is of the order of 1.8–2.6 (7) then if scheme (i) is applicable one would expect the 2,3- to 2,5-isomer ratio to be substantially higher with 3-picoline than when 3-picoline-2d was used. This was not found to be the case, the observed isomer ratio being 95:5 in both cases (under otherwise identical conditions). It is clear, therefore, that the rate of hydride ion elimination is not important in determining the observed orientation.

Finally, an excess of a mixture of pyridine and pyridine-2d was allowed to react with a small amount of phenyllithium in the presence of an excess of anhydrous lithium bromide. Unreacted pyridine–pyridine-2d mixture was recovered from this competitive reaction and analyzed for pyridine-2d using an infrared spectroscopic method (see Experimental). A blank run was carried out using identical conditions except that the phenyllithium was

(c) *In the presence of an excess of lithium bromide.*—The procedure was essentially the same as that described under (a) or (b), respectively, except that two molar equivalents of anhydrous lithium bromide in dry ether were added per mole of pyridine used. No appreciable evolution of heat was observed when the phenyllithium solution was added. Some typical results are summarized in Table I.

(d) *Using halide-free phenyllithium.*—The procedure was identical with that used under methods (a) or (b). A vigorous exothermic reaction took place when the phenyllithium solution was added to the pyridine. A few of the results are given in Table I.

Reaction of Halide-free Phenyllithium with 3-Picoline-2d

The addition of halide-free phenyllithium was carried out as described under (a) above except that 3-picoline-2d (10) (0.2 g, 0.0021 moles; 11.67 atom % D) was used. To this was added 0.001 moles of phenyllithium in dry ether. The yield of products was 18.6% and the ratio of 2,3- to 2,5-isomer was 95:5.

Oxidation of Dihydrophenylpicolines

(a) A solution of phenyllithium (0.023 moles) in ether (30 ml) was added dropwise with stirring under nitrogen to a solution of 3-picoline (5.58 g, 0.06 moles) in ether (10 ml), at such a rate that the temperature of the reaction mixture did not rise appreciably. It was then immediately cooled to $-10°$, treated cautiously with an excess of iced water, the ether layer separated, and the aqueous layer extracted with ether. The combined ether extracts were added with stirring to a solution of chloranil (14.6 g) in benzene (600 ml) and filtered. The residue was washed with ether and the combined washings and filtrate were concentrated down to a small volume (2 ml) and analyzed by gas chromatography. The combined yield of 3-methyl- and 5-methyl-2-phenylpyridine was 19.0%; the isomer ratio was 96:4.

(b) In this experiment the mixture obtained above after treatment with water was not extracted with ether but was treated directly with a benzene solution of chloranil and analyzed. The ratio of 2,3- to 2,5-isomer was 94:6 and the combined yield was 22.5%.

Reaction of Phenyllithium with Pyridine–Pyridine-2d Mixture

A solution of 'ordinary' phenyllithium (0.018 moles) in anhydrous ether (66 ml) was added dropwise at 24°, and under oxygen-free dry nitrogen to a well stirred solution of anhydrous lithium bromide (0.076 moles), pyridine (0.0179 moles), and pyridine-2d (10) (0.0201 moles) in anhydrous ether (150 ml). At the end of the addition, stirring was continued for another 2 hours, oxygen was bubbled through the mixture for 5–10 minutes, the suspension treated with an excess of water, and the mixture of recovered pyridine and pyridine-2d isolated and purified by preparative gas-chromatography on columns of silicone oil (25%) on Fisher Columnpak (60–80 mesh) at 70°. The mixture was then dried (KOH pellets) and distilled.

A blank run was carried out similarly except that the phenyllithium was omitted. The composition of the recovered pyridine–pyridine-2d was used for comparison with the recovered material from the actual runs.

The quantitative analyses for pyridine-2d were carried out by determining the infrared spectra of authentic mixtures of known concentration of pyridine and pyridine-2d (as pure liquids) in matched 1-mm fixed-thickness cells. A calibration curve for the pyridine-2d concentration was obtained by plotting log T (where T = % transmission) of the C—D stretching band at 2260 cm^{-1} against the corresponding known concentration of pyridine-2d, and was a straight line, thus making it unnecessary to measure the areas under the C—D band.

In all runs, the composition of the recovered pyridine–pyridine-2d mixture was identical with that of the starting material.

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