AROMATIC SUBSTITUTION

PART I. THE REACTION OF PHENYLLITHIUM WITH 3-ALKYLPYRIDINES. STERIC EFFECT AND QUANTITATIVE ANALYSIS OF ISOMER RATIOS[1]

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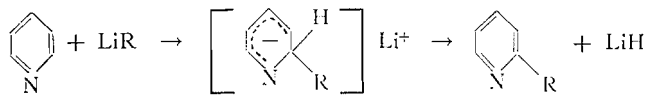
ABSTRACT

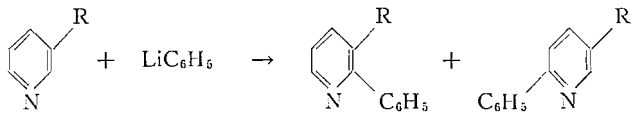
No 4-phenylpyridine is formed in the reaction of phenyllithium with pyridine. When phenyllithium reacts with a 3-alkylpyridine the main product is the 3-alkyl-2-phenylpyridine if the alkyl group is methyl, ethyl, or isopropyl, but it is the 5-alkyl-2-phenylpyridine when the substituent is *t*-butyl. Methods are described for the separation and quantitative analysis of mixtures of 3-alkyl- and 5-alkyl-2-phenylpyridines using vapor phase chromatography. The results are discussed briefly and possible explanations of the observed orientations are mentioned.

The well-known (1, 2) reaction of lithium alkyls and aryls with dry pyridine involves the formation of a dihydroderivative (I) which, on heating, eliminates lithium hydride to give the 2-substituted pyridine (3):



I

The formation of a 4-substituted pyridine has not been reported in such reactions except in those cases where the 2- and 6-positions of the pyridine ring are blocked, e.g. the case of acridine (4). It has now been verified that in the reaction of phenyllithium with pyridine no 4-phenylpyridine can be detected, even by vapor phase chromatography. Thus, the addition of an organo-lithium compound to a 3-substituted pyridine may lead to one isomer, or a mixture of two isomers:



II III IV

In two earlier papers (5, 6) the reaction of phenyllithium with a number of 3-substituted pyridines was examined. When 3-picoline (II; R = CH_3) was treated with phenyllithium the ratio of 2,3:2,5 isomers was found to be 19:1. With nicotine (II; R = 2-*N*-methylpyrrolidyl) the isomer ratio was approximately 1:1. Two further examples were studied: R = NH_2 and R = OCH_3. In both cases the only isomer detected was the 2,3-disubstituted pyridine. It was suggested (6) that in these last two cases the exclusive substitution at the 2-position might be explained by assuming some co-ordination of the lithium atom with a pair of electrons on the 3-substituent such that the phenyl group would be suitably oriented for attack at the 2-position.

[1]*This paper was presented as part of a lecture given at the Stereochemistry Symposium of the C.I.C. at Edmonton in September 1960.*

The preferential attack of the 2-position by the nucleophilic reagent in these and other reactions (for a brief summary of previous work on related reactions see ref. 5) was contrary to what would have been predicted a priori on the basis of a consideration of straightforward electronic and steric effects of the substituents studied. One would expect the 2-position to be somewhat more electron rich than the 6-position and also that attack at that site would be subject to the steric effect of the 3-substituent. That the 3-substituent does exert a steric effect is shown by a comparison of the isomer ratios for the reactions of 3-picoline and of nicotine. Appreciable steric hindrance by an ortho-methyl group in nucleophilic aromatic substitutions has also been observed in the reaction of 1-chloro-2,4-dinitro-6-methylbenzene with piperidine (7), though the geometry of the transition state is probably different from that in our reactions, which involve a more powerful nucleophilic reagent in a less polar solvent. It seems likely that with the more powerful nucleophilic reagent the transition state would resemble the reactants and that its formation would not lead to too much perturbation of the π-electron densities in the ground state (8, 9) (in which case hyperconjugation by the 3-alkyl group would probably be small).

It was clearly of interest to examine the effect of increasing the size of the 3-alkyl group systematically from methyl to *t*-butyl upon the ratio of III:IV obtained and this has now been done.

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were measured with a Perkin–Elmer Model 21 instrument using sodium chloride optics; only the main peaks are reported. Vapor phase chromatography was carried out with a Beckman GC-2 unit fitted with a fraction collector and modified such that the heated sample inlet block permitted injection as close to the column as possible.

Preparation of 3-Alkylpyridines

3-Picoline was commercially available synthetic material (Reilly Tar and Chemical Corp.); this was dried (KOH) and distilled through a Podbielniak Mini-Cal Spinning Band Column, the fraction b.p. 138–140° at 720 mm being used.

3-Ethylpyridine was prepared by the alkylation of 3-picoline as described by Brown and Murphey (10). An average yield of 50.4% was obtained. However, even after several fractional distillations through a Podbielniak column, the 3-ethylpyridine could not be isolated in a completely pure state; it was always contaminated with small amounts of 3-picoline and 3-isopropylpyridine, as indicated by vapor phase chromatography. Since the 3-ethylpyridine required had to be essentially free of these contaminants it was prepared from 3-acetylpyridine using hydrazine hydrate and potassium hydroxide (11). A yield of 83.5% of pure product was thus obtained.

3-Isopropylpyridine was obtained initially as a by-product of the alkylation of 3-picoline (average yield 10%). When 3-ethylpyridine was the starting material the average yield was raised to 55%; the product, however, could not be freed from 3-ethylpyridine completely by fractional distillation. Pure 3-isopropylpyridine was, therefore, prepared from methyl nicotinate by treating the latter with methyl magnesium iodide (12), dehydrating the alcohol obtained with a mixture of concentrated sulphuric acid and acetic acid (10), and hydrogenating the resulting 3-isopropenylpyridine (in solution in a mixture of glacial acetic acid (1 part) and 95% ethanol (4 parts)) at 25 p.s.i. and room temperature in the presence of Adams' catalyst.

3-*t*-Butylpyridine was prepared by a modification (13) of the method for the alkylation of 3-isopropylpyridine. The time of addition of the methyl chloride was extended to 13 hours. In no case could a conversion of more than 10% be achieved, though Professor Brown informs us that he has obtained yields as high as 37%. Essery and Schofield (14) have recently also been unable to obtain such a high yield using potassium amide instead of sodamide in liquid ammonia. In spite of repeated and careful fractional distillations the product obtained was only 95% pure and had to be used as such in subsequent reactions with phenyllithium.

2-Phenylpyridine (2)

A solution of pyridine (0.93 g) in dry ether (2 ml) was added to a well-stirred, standardized ethereal solution of phenyllithium (6 ml, 0.007 mole) under nitrogen and worked up by the general procedure described below. The crude reaction product was subjected to vapor phase chromatography on a column 3 ft$\times\frac{1}{4}$ in. of "Apiezon N" on "Embacel" (May and Baker), the column temperature being 190° and the helium inlet pressure 50 p.s.i. The product had the same retention time as authentic 2-phenylpyridine (8 minutes, 10 seconds). No peak corresponding to 4-phenylpyridine (9 minutes, 30 seconds) was observed. It was verified that small amounts of 4-phenylpyridine would have been detected by this method by analyzing made-up mixture of authentic samples of 2- and 4-phenylpyridine. Purification of the crude reaction product gave 2-phenylpyridine (0.76 g; 69%).

Reaction of Phenyllithium with 3-Alkylpyridines

The procedure described below was adopted for all the reactions of phenyllithium with 3-picoline, 3-ethyl-, 3-isopropyl-, and 3-*t*-butyl-pyridine. The amounts of the reactants employed and the yields of products obtained are summarized in Table I.

TABLE I

Reaction of phenyllithium with 3-alkylpyridines

Expt. No.	3-Alkyl substituent	Wt. of lithium (g)	Wt. of bromobenzene (g)	Wt. of 3-alkylpyridine (g)	Total % yield of both isomers
1	CH_3	30.0	313.8	204	(*b*)
2	CH_3	0.15	1.05	1.02	41.6
3	CH_3	0.15	1.05	1.02	25.0
4	CH_3	(*a*)	(*a*)	(*a*)	41.6
5	C_2H_5	6.9	52.5	58.9	20.5
6	C_2H_5	0.15	1.05	1.10	22.9
7	C_2H_5	0.15	1.05	1.10	18.0
8	C_2H_5	(*a*)	(*a*)	(*a*)	39.4
9	iso-C_3H_7	0.28	2.1	2.66	(*b*)
10	iso-C_3H_7	3.8	28.8	33.2	15.0
11	iso-C_3H_7	(*a*)	(*a*)	(*a*)	25.2
12	*t*-C_4H_9	0.30	2.1	2.96	22.5
13	*t*-C_4H_9	1.89	13.1	18.7	25.0
14	*t*-C_4H_9	(*a*)	(*a*)	(*a*)	24.2

NOTE: (*a*) In these experiments, 0.007 mole of phenyllithium and 0.010 mole of 3-alkylpyridine were used.
(*b*) Yields in these experiments were not determined.

Very finely cut lithium was suspended in anhydrous ether (approximately 300 ml for each mole of lithium) under dry nitrogen and to this was added dropwise a solution of bromobenzene in an equal volume of dry ether. Gentle reflux was continued for 3 hours after which a solution of the 3-alkylpyridine in dry ether was added dropwise so that boiling under gentle reflux was maintained. When the addition was completed the ether was distilled off and simultaneously replaced by an equal volume of dry toluene. The temperature of the reaction mixture was then raised to ca. 110° and kept there for 7½ hours. The mixture was cooled, treated cautiously with an excess of water, and exhaustively extracted with ether. The ether extract was dried (KOH) and the solvent removed by distillation. The residue was divided into two portions, the larger one being used for the isolation and identification of the reaction products and the smaller being used for the quantitative analyses of the isomeric alkylphenylpyridines.

Isolation of the 3-Alkylpyridines

The isomeric alkylphenylpyridines were separated and isolated by preparative vapor phase chromatography. In experiments (1) and (2) a copper tubing column 5½ ft × ¼ in. (I.D.) packed with "Apiezon N" on "Embacel" Kieselguhr (1:4 by weight) was used. In all the other experiments, four 10-in. columns (½ in. I.D.) connected in series and packed with "Apiezon N" on Celite 545 (1:4 by weight) were used.

Differentiation between 3-Alkyl- and 5-Alkyl-2-phenylpyridines by Infrared Spectroscopy

The isomeric alkylphenylpyridines could be characterized by using their infrared spectra as described by Abramovitch, Giam, and Notation (15). The 3-alkyl-2-phenylpyridines exhibited a characteristic absorption band in the range 1577–1589 cm^{-1}, and the 5-alkyl-2-phenylpyridines gave a band in the range 1592–1605 cm^{-1}. Assignment of orientation could also be made from a study of the range 900–750 cm^{-1} as discussed by Podall (16).

Some of the assignments were confirmed by oxidation of the isomers to known compounds and by the behavior on vapor phase chromatography (see below). In the case of the methylphenylpyridines n.m.r. spectroscopy has also been used (5).

3-Ethyl-2-phenylpyridine

B.p. 156–158° at 18 mm. Infrared spectrum (liquid film): 1583 (m), 1568 (m), 1435 (s), 1060 (m), 793 (s), 750 (s), 698 cm^{-1} (s). Calc. for $C_{13}H_{13}N$: C, 85.20; H, 7.15. Found: C, 85.26; H, 7.22. The product was identical with that obtained from authentic 3-methyl-2-phenylpyridine as described below. The picrate was recrystallized from benzene and had m.p. 104°. Calc. for $C_{13}H_{13}N,C_6H_3O_7N_3$: C, 55.34; H, 3.91. Found: C, 55.46; H, 3.96.

5-Ethyl-2-phenylpyridine

B.p. 179–180° at 22 mm. Infrared spectrum (liquid film): 1603 (m), 1567 (m), 1483 (s), 1440 (s), 842 (m), 793 (m), 742 (s), 695 cm^{-1} (s). Found: C, 84.81; H, 7.36. The picrate (from benzene) had m.p. 155–156°; found: C, 55.74; H, 4.04.

3-Isopropyl-2-phenylpyridine

B.p. 152–154° at 22 mm. Infrared spectrum (liquid film): 1580 (m), 1563 (m), 1436 (s), 1385 (m), 1367 (m), 793 (s), 750 (s), 698 cm^{-1} (s). Calc. for $C_{14}H_{15}N$: C, 85.23; H, 7.66. Found: C, 85.28; H, 7.61.

5-Isopropyl-2-phenylpyridine

White crystals, m.p. 53–53.5° (purified by sublimation after vapor phase chromatography). Infrared spectrum (Nujol mull): 1595 (m), 1561 (m), 842 (s), 787 (m), 737 (m), 693 cm^{-1} (s). Found: C, 85.17; H, 7.78.

3-t-Butyl-2-phenylpyridine

B.p. 140° at 18 mm. Infrared spectrum (liquid film): 1578 (w), 1561 (m), 1427 (s), 1395 (w), 1365 (m), 785 (s), 762 (s), 702 cm^{-1} (s). Calc. for $C_{15}H_{17}N$: C, 85.26; H, 8.11. Found: C, 84.90; H, 8.30.

5-t-Butyl-2-phenylpyridine

B.p. 130° at 0.72 mm. Infrared spectrum (liquid film): 1592 (m), 1535 (m), 1480 (s), 1377 (s), 1395 (w), 1365 (w), 845 (s), 750 (s), 730 (s), 690 cm^{-1} (s). Found: C, 85.32; H, 8.18.

A plot of the logarithm of the retention times against the number of carbon atoms in the side-chain alkyl groups in 3-alkyl-2-phenylpyridines gave a straight line as did the corresponding plot of the values for 5-alkyl-2-phenylpyridines. The slope of the latter line was greater than that of the former. This observed linearity in each case serves as confirmatory evidence for the orientation assigned to the various pairs of isomers.

Oxidation of 5-Ethyl-2-phenylpyridine

5-Ethyl-2-phenylpyridine was boiled under reflux with an aqueous solution of potassium permanganate for 8 hours and worked up as described for the oxidation of 3-methyl-2-phenylpyridine (5). 2-Phenylpyridine-5-carboxylic acid, m.p. 232°, was obtained. The melting point was undepressed on admixture with an authentic specimen of this acid (5).

Synthesis of 3-Ethyl-2-phenylpyridine

3-Methyl-2-phenylpyridine (6.9 g) was added to a suspension of sodamide in liquid ammonia (2.3 g of sodium in 80 ml of anhydrous ammonia and 0.03 g of ferric nitrate nonahydrate), followed by methyl chloride (5 g), the addition of the latter taking approximately 15 minutes. The mixture was allowed to stand overnight when the ammonia evaporated and the residue was cautiously treated with water and exhaustively extracted with ether. The ether extract was dried (KOH), the solvent evaporated, and the residue fractionally distilled under vacuum. The fraction b.p. 110–143° at 11 mm was subjected to vapor phase chromatography using a copper column, $5\frac{1}{2}$ ft × $\frac{1}{4}$ in. (I.D.), packed with "Apiezon N" on "Embacel" (1:4 by weight), the column temperature being 220°. A compound having the same "emergence time" (the time taken for the compound to begin entering the detector cell) as the sample of 3-ethyl-2-phenylpyridine obtained from the reaction of phenyllithium with 3-ethylpyridine was isolated. This compound had an infrared spectrum identical with that of the compound which had been assigned the structure 3-ethyl-2-phenylpyridine on the basis of its infrared spectrum. Both samples formed picrates whose melting points (102–103°) were undepressed on admixture. In the alkylation reaction a 33% conversion of 3-methyl-2-phenylpyridine to 3-ethyl-2-phenylpyridine (2.2 g) was achieved.

Quantitative Analyses

Once the various isomeric alkylphenylpyridines had been isolated and characterized calibration curves were prepared for each individual isomer so that its concentration in a mixture could be estimated from the area under the curve of its vapor phase chromatogram. A linear plot of the areas of their chromatograms versus concentration was obtained for the individual isomers as well as for a number of made-up mixtures of known concentrations of isomeric pairs. The concentrations of the isomers formed during the phenylation reactions could then be read off from the calibration curves, provided the conditions established for the chromatographic analysis of each pair of isomers were kept constant. These conditions are summarized below:

Methylphenylpyridines: $5\frac{1}{2}$ ft × $\frac{1}{4}$ in. (I.D.) copper tube packed with "Apiezon N" on "Embacel" (1:4 by weight); column temperature 220°; helium inlet pressure 30 p.s.i.

Ethylphenylpyridines: same conditions as for methylphenylpyridines.

Isopropylphenylpyridines: 2 ft × $\frac{1}{4}$ in. (I.D.) copper tube packed with "Apiezon N" on Celite 545 (1:4 by weight); column temperature 220°; helium inlet pressure 40 p.s.i.

t-Butylphenylpyridines: 3 ft × $\frac{1}{4}$ in. (I.D.) copper tube packed with "Apiezon N" on "Embacel" (1:4 by weight); column temperature 220°; helium inlet pressure 30 p.s.i.

The results of the quantitative analyses are summarized in Table II, which also contains the data for the reaction of nicotine with phenyllithium (5).

DISCUSSION OF RESULTS

The results given in Table II indicate that the 3-substituent exerts a slight steric effect which becomes quite large when the alkyl group is *t*-butyl. The sudden great increase in steric hindrance to attack at the 2-position on passing from 3-iso-C_3H_7 to 3-*t*-Bu is unexceptional

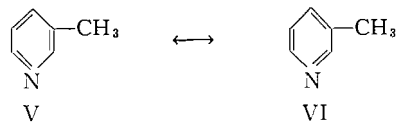
TABLE II
Ratio of III:IV in the reaction of C_6H_5Li with 3-RC_5H_4N

R	III:IV	No. of runs
CH_3	94.6:5.4 (±0.6)	4
C_2H_5	84.0:16.0 (±0.5)	4
iso-C_3H_7	70.0:30.0 (±4.0)	3
t-C_4H_9	4.5:95.5 (±0.5)	3
2-*N*-Methylpyrrolidyl (5)	49.6:50.4 (±0.2)	2

(17). The fact that the steric effect of the lower alkyl group is only relatively small seems to confirm the suggestion made above that in the transition state leading to the formation of the dihydroderivative the attacking phenyl group is almost perpendicular to the pyridine ring, whose ground-state configuration is only slightly distorted. The results also indicate quite strikingly that in spite of the greater deactivating influence of the +I effect of the alkyl group on the 2- than on the 6-position and some steric hindrance to attack at the 2-position, addition of the nucleophilic reagent takes place preferentially at that carbon atom. In fact, in the case of 3-picoline the ortho/para ratio (with respect to methyl) is as high as 19. This "ortho" effect is reminiscent of those encountered in electrophilic substitutions on compounds bearing substituents such as —NO_2, —CO_2H, —CN, and so on. Similar results to those reported above have been obtained by Brown and his group but using methyllithium instead of phenyllithium (13).

No decision can be made as to the correct explanation of the observed substitution pattern since too little is known about the detailed mechanism of this addition–elimination reaction and the effect of various substituents upon the rates and orientation in such nucleophilic substitutions. Both of these aspects are presently under investigation in these laboratories and the results of such studies should permit a clearer formulation to be made of the mechanisms involved. It is of interest though, to speculate a little about possible explanations of the orientation observed.

There is only one published molecular orbital calculation of the π-electron densities at the various nuclear carbon atoms in the ground state of 3-picoline, that due to Ploquin (18). Dr. K. L. McEwen has kindly repeated for us Ploquin's calculation for several different values of the nitrogen and methyl group inductive parameters. The results indicate that the 2-position would be slightly more favorable than position 6 for nucleophilic attack only if a negative inductive effect (−I) is attributed to the methyl group. With a positive inductive effect attack at the 6-position would be favored over attack at the 2-position. The introduction of methyl hyperconjugation into the ground-state calculations made little difference to the results. The nucleophilic localization energies at C_2 and C_6 were not calculated but if the postulate that the geometry of the transition state is more related to that of the ground state than to that of the intermediate is correct then these would not enter into the picture. A −I effect for methyl has been suggested by Murrell and McEwen to explain the observed shifts in the ultraviolet absorption spectra of some substituted benzenes (19). There is, however, a large body of chemical and physicochemical evidence which indicates that alkyl groups have a +I effect. Indeed, the n.m.r. spectrum of 3-picoline itself is consistent with the effect of the higher electron density in the ring due to the presence of the methyl substituent (20). Another possible explanation involves the contributions made by each of the two Kékulé structures V ↔ VI to the actual state of the 3-picoline molecule. If one assumes that the electrical effect of the 3-methyl substituent is such as to stabilize structure V with respect to VI, then V would have a larger coefficient than VI in the aromatic wave function, and



V VI

direction of a polar effect would be that which V would favor. If one then assumes that the phenyl anion (if such is the attacking species) will add at that end of the conjugated system whose other end is the N atom, then addition should take place preferentially at the 2-position.* It is not clear at the moment how an alkyl group would favor the stabilization of V with respect to VI. Yet another explanation possible would involve the hyperconjugation by the methyl group. Structure VIII, being *p*-quinonoïd in nature, might be more stable than VII so that the electron density at the 2-position would consequently

VII VIII

be less than at the 6-position. Similar arguments have been used to explain the high ortho/para ratios observed in the nitration of nitrobenzene and benzonitrile, for example ref. 21. Two further possibilities have to be taken seriously into account: one is that there may be some form of *steric acceleration* favoring substitution at the 2-position and not at the 6-position (the nitrogen atom in the picoline is obviously complexed in some way either with phenyllithium itself or with the lithium bromide present in solution and this would have the same steric effect as a substituent on the N atom). The other is some form of attractive interaction, perhaps of the nature of London dispersion forces, between the polarizable approaching nucleophile and the methyl substituent which would accelerate attack ortho to the methyl group rather than para to it. Dipolar field effects have been similarly suggested to explain the high ortho/para ratios in electrophilic substitutions mentioned above (22). This seems to be a very attractive possibility in the present case and is being investigated.

It should be pointed out that if the second stage in this reaction, the elimination of hydride ion, should be rate-determining, and if it is assumed that the addition step is rapidly reversible, a simple explanation is possible for the observed orientation. The transition state for such an elimination probably involves the abstraction by the lithium cation of the hydrogen atom with its bonding pair of electrons and the electron-repelling ortho-alkyl group should lower the energy of this transition state more than would a para-alkyl substituent.† At present, work is in progress to try to establish which step is the rate-determining one in this reaction, as well as to clarify the effect of alkyl substituents (activating or deactivating), the effect of the lithium bromide present in solution in this particular case, and the effect of quaternizing the ring nitrogen atom. There are some data in the literature on the last point. For example, in the reaction of 3,4-lutidine methiodide with benzyl magnesium chloride the only isomer formed was apparently the 1,2-dihydroderivative (23). Other examples of such reactions are known (24).

The authors would like to express their gratitude to Professor C. K. Ingold for a discussion of this point.

†*A referee has pointed out, however, that hydride expulsion from the ortho-substituted addition product should be less favorable on steric grounds than from the para-substituted addition product since in the former, formation of the transition state brings the alkyl and phenyl substituents closer together. We wish to thank the referee for bringing this to our attention.*

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