AROMATIC SUBSTITUTION

XIV. THE HOMOLYTIC PHENYLATION OF 3- AND 4-PICOLINE. A QUANTITATIVE STUDY OF ISOMER AND TOTAL RATE RATIOS[1]

R. A. Abramovitch and Maitreyi Saha
Department of Chemistry, University of Saskatchewan, Saskatoon, Saskatchewan
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ABSTRACT

The homolytic phenylation of 3- and 4-picoline under the conditions of the Gomberg–Hey reaction has been studied quantitatively. The methyl group in both picolines was found to activate the nucleus to the same extent. All the nuclear positions in both systems, except for C_5 in 3-picoline, were slightly activated as compared with any one position in benzene. The significance of these results is discussed.

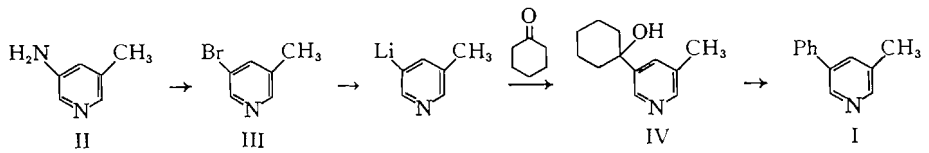
In previous parts of this series (1, 2), the effects of substituents in the aryl radical upon the isomer ratio and upon the relative reactivities of the nuclear positions in pyridine towards free-radical arylation have been studied. On the other hand, the effects of substituents present in the pyridine nucleus upon the reactivity of the various positions towards homolytic attack have received little attention. A qualitative analysis of the products formed in the substitution of 4-picoline by 3-pyridyl radicals showed that both the 2- and 3-(3′-pyridyl) isomers were formed in the ratio of 3:11 (3). Similar results were obtained with 4-ethylpyridine (3). Ethyl isonicotinate is reported to give only ethyl 2-(3′-quinolyl)isonicotinate with the 3-quinolyl radical (4). The alkylation of 3-picoline by methyl radicals (from lead tetraacetate) is said to give a mixture of 2,3- and 2,5-lutidine (5), though the other isomers are undoubtedly present as well (6). Methylation of 3-*n*-butylpyridine with lead tetraacetate in acetic acid (in which the pyridine is undoubtedly *N*-protonated to a large extent) has been examined semiquantitatively (7). The main product of monomethylation (60% of total) was 3-*n*-butyl-2-methylpyridine, and about equal amounts (slightly less than 20%) of each of the 4- and 6-methyl derivatives were obtained. About 2% of the total product was thought to consist of 3-*n*-butyl-5-methylpyridine. A small amount of the dimethylated 3-*n*-butylpyridines was obtained together with an appreciable quantity of a high-boiling residue.

The present work reports a quantitative study of the homolytic phenylation of 3- and 4-picoline under the conditions of the Gomberg–Hey reaction. Since the reactivities of the various nuclear positions of pyridine (1) and toluene (8, 9) towards attack by phenyl radicals are known, it was of interest to determine whether the effects of the nitrogen atom and of the methyl group in the picolines were additive in this reaction.

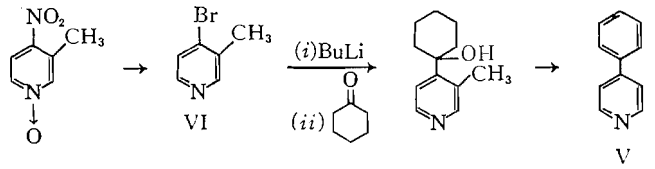
Of the possible products from the phenylation of 3-picoline, 4-phenyl-3-picoline was not known. 5-Phenyl-3-picoline (I) had previously been prepared by the condensation of phenylacetaldehyde, propionaldehyde, and ammonia, and had been obtained as a mixture with 3,5-diphenylpyridine, 3,5-diphenyl-2-ethylpyridine, and 2-ethyl-3-methyl-5-phenylpyridine (10). A more conventional approach to this compound was used here, starting with 3-methyl-5-pyridyllithium and cyclohexanone. 5-Bromo-3-picoline (III) was required and was prepared from 5-amino-3-picoline (II) by the Craig perbromide procedure. An attempt to make use of the Gattermann reaction for this purpose gave a basic product

[1]*For part XIII in this series, see ref. 2.*

whose picrate did not analyze correctly for that of III. When the bromination of 3-picoline with bromine and aluminium chloride (swamping catalyst method (11)) was carried out, a mixture of three products was obtained, more than 85% of which was 5-bromo-3-picoline. The formation of I from 1-(3′-methyl-5′-pyridyl)cyclohexanol (IV) with concentrated sulfuric acid and glacial acetic acid was unexceptional.



4-Phenyl-3-picoline (V) was prepared similarly from 3-methyl-4-pyridyllithium and cyclohexanone. A number of attempts were made at preparing pure 4-bromo-3-picoline (VI). 4-Bromo-3-picoline 1-oxide, m.p. 112–113° (reported (12) m.p. 72–73°), decomposed very readily and could not be used conveniently. Reduction of 4-nitro-3-picoline 1-oxide with iron and acetic acid gave 4-amino-3-picoline which, in turn, gave 4-bromo-3-picoline (VI) by the Craig method. The yields of VI were very poor and the compound obtained in this way underwent self-addition very readily, a process probably catalyzed by some impurity that was present. On the other hand, a reasonably good yield (47%) of VI was obtained on treatment of 4-nitro-3-picoline 1-oxide with phosphorus tribromide in ethyl acetate. The product could be distilled without decomposition.



EXPERIMENTAL

Melting points are uncorrected. Only the main peaks are reported for the infrared spectra.

5-Bromo-3-picoline

(a) From 5-Amino-3-picoline

A solution of 5-amino-3-picoline (2.0 g) (13) in constant-boiling hydrobromic acid (8.0 ml) was treated with bromine (2.4 ml) dropwise at 0°, stirring was continued for 15 min, and then a solution of sodium nitrite (4.0 g) in water (12.0 ml) was added at such a rate as to keep the temperature at 0–5°. A vigorous evolution of gas occurred at the end of the addition. When the effervescence had subsided the mixture was made alkaline and then steam-distilled. The distillate was extracted with ether, the ethereal layer was dried (Na_2SO_4) and evaporated, and the residue was distilled to give 5-bromo-3-picoline (1.38 g), b.p. 108–110° at 25 mm. Infrared spectrum (liquid film): 1 595 (m), 1 445 (s), 1 165 (m), 1 105 (s), 1 035 (s), 1 005 (w), 870 (s), 860 (s), 700 (s), and 665 (w) cm^{-1}. The picrate crystallized from ethanol and was recrystallized from the same solvent. It had m.p. 180–181°.

Anal. Found: C, 36.25; H, 2.47. $C_6H_6NBr \cdot C_6H_3N_3O_7$ requires C, 35.91; H, 2.24.

The use of the Gattermann reaction in the synthesis of this compound gave a very impure material which did not analyze correctly.

(b) By the Swamping Catalyst Method

Anhydrous 3-picoline (4 g, 0.041 mole) was added dropwise to stirred anhydrous aluminium chloride (14 g, 0.103 mole) (calcium chloride guard tube). Heat was evolved and bromine (4.0 g) was added to the mixture over a period of 1.5 h while the temperature was maintained at 95–100°. After being kept at room temperature overnight the mixture was decomposed with ice water, made alkaline, and extracted with ether. The ether layer was dried ($MgSO_4$), the solvent evaporated, and the residue distilled at 112–114° and 60 mm to give a yellow oil (1.22 g). This was analyzed by gas chromatography with a 6 ft × ¼ inch 15% asphalt on Chromosorb W column operated at 165° and a helium inlet pressure of 45 p.s.i. Three peaks were observed; the substance giving rise to the major peak (>85%) was collected and shown to be identical with 5-bromo-3-picoline by a comparison of its infrared spectrum with that of a sample prepared by method *a* above.

The attempted bromination of 3-picoline in the presence of thionyl chloride gave a complex mixture of at least four products which was not examined further.

1-(3′-Methyl-5′-pyridyl)cyclohexanol

A solution of *n*-butyllithium in hexane (3.5 ml of a 14.9% solution) and dry ether (2.0 ml) was stirred vigorously under dry, oxygen-free nitrogen and cooled to −62° to −74°. 5-Bromo-3-picoline (1.0 g) in dry ether (2.0 ml) was added dropwise over a period of 15 min, the mixture was stirred for a further 15 min, and a solution of freshly distilled cyclohexanone (3.0 ml) in dry ether (2.0 ml) was then added slowly during 30 min. After being stirred for another 3 h at −62° to −74° the reaction mixture was allowed to come to room temperature, poured onto crushed ice, and extracted with ether. The dried ($MgSO_4$) ether extract was evaporated to give 1-(3′-methyl-5′-pyridyl)cyclohexanol (0.97 g) which, after recrystallization from acetone, had m.p. 144–144.5°. Infrared spectrum (KBr disk): 3 250 (s), 1 595 (m), 1 440 (s), 1 395 (s), 1 320 (m), 1 272 (s), 1 180 (s), 1 145 (s), 1 045 (s), 995 (s), 870 (s), 815 (m), 795 (w), 715 (s), and 695 (w) cm^{-1}.

Anal. Found: C, 74.94; H, 8.97. $C_{12}H_{17}NO$ requires C, 75.35; H, 8.96.

5-Phenyl-3-picoline

1-(3′-Methyl-5′-pyridyl)cyclohexanol (0.2 g) was boiled under reflux with a mixture of concentrated sulfuric acid (1.0 ml) and glacial acetic acid (3.0 ml) for 4 h. Most of the acetic acid was then distilled off, the residue was poured into water, and the solution was made basic and extracted with ether. The dried ($MgSO_4$) ether extract was evaporated and the residue distilled to give 5-phenyl-3-picoline (0.14 g), b.p. 208–210° at 60 mm. Infrared spectrum (liquid film): 3 070 (m), 1 505 (w), 1 425 (m), 1 155 (m), 1 035 (m), 840 (m), 815 (s), 760 (s), 710 (s), 695 (s), and 660 (w) cm^{-1}. The picrate was recrystallized from ethanol and had m.p. 200–201°. Farley and Eliel (10) give m.p. 191–192° for this picrate.

Anal. Found: C, 53.80; H, 3.88. $C_{12}H_{11}N \cdot C_6H_3N_3O_7$ requires C, 54.27; H, 3.54.

3-Benzylpyridine

Because the red phosphorus and hydriodic acid method of reduction of 3-benzoylpyridine (14) proved to be unsatisfactory in our hands, a Wolff–Kishner reduction was used.

3-Benzoylpyridine (3.6 g) was dissolved in diethylene glycol (30.0 ml), and 90% hydrazine hydrate (3.0 ml) and potassium hydroxide (4.0 g) were added. The mixture was boiled under reflux for 6–7 h, cooled, and extracted with ether. The dried ($MgSO_4$) ether layer was evaporated and the residue distilled. The fraction (0.92 g), b.p. 285–288°, crystallized in the refrigerator and gave a picrate, m.p. 124–126° when crystallized from ethanol. Tschitschibabin (14) reported m.p. 34° for 3-benzylpyridine and m.p. 126–127° for its picrate.

4-Bromo-3-picoline 1-Oxide

4-Nitro-3-picoline 1-oxide (1.0 g) (15) was heated under reflux with constant-boiling hydrobromic acid (40 ml) for 24 h. The reaction mixture was poured onto crushed ice and neutralized with aqueous sodium hydroxide. The product was extracted with chloroform, the extract dried (Na_2CO_3), and the solvent evaporated to give a light-yellow solid (0.92 g) which, after recrystallization from light petroleum (b.p. 60–80°), gave fine white needles of the bromo *N*-oxide, m.p. 112–113°. Infrared spectrum (KBr disk): 3 400 (m, br), 1 450 (s), 1 400 (s), 1 390 (w), 1 290 (s), 1 245 (s), 1 205 (m), 1 155 (s), 1 005 (m), 850 (w), 845 (w), 835 (w), 745 (s), and 695 (m) cm^{-1}.

Anal. Found: C, 38.80; H, 3.51. C_6H_6NOBr requires C, 38.32; H, 3.19.

Hai and Ogura (12) reported m.p. 72–73° for this compound. The picrate was recrystallized from benzene and had m.p. 117–118°, depressed on admixture with picric acid.

4-Bromo-3-picoline

(a) By the Craig Procedure

4-Amino-3-picoline (2.0 g) (15) in constant-boiling hydrobromic acid (8 ml) was cooled to 0° and treated with bromine (2.4 ml) dropwise. Stirring at 0° was continued for 15 min, and a solution of sodium nitrite (4.0 g) in water (12 ml) was then stirred in at such a rate that the temperature of the mixture remained at 0–5°. At the end of the addition a vigorous evolution of gas occurred. The solution was made basic with 10% sodium hydroxide solution, the temperature not being allowed to rise above 25°, and then steam-distilled. The distillate was extracted with ether, the organic layer dried ($MgSO_4$), and the solvent evaporated. The residue was distilled to give 4-bromo-3-picoline (0.185 g, 5.8%), b.p. 108–110° at 60 mm. The picrate (crystallized from benzene) was recrystallized from ethanol and had m.p. 139–141°.

Anal. Found: C, 35.75; H, 2.55. $C_6H_6NBr \cdot C_6H_3N_3O_7$ requires C, 35.91; H, 2.24.

(b) From 4-Nitro-3-picoline 1-Oxide

Phosphorus tribromide (36.0 g) was added to a mixture of 4-nitro-3-picoline 1-oxide (5.0 g) and dry ethyl acetate (300 ml), and the mixture was boiled under reflux for 30 min. The reaction mixture was poured into water and the solution extracted with ether. The aqueous layer was made alkaline, care being taken to maintain the temperature at 25–30°. The solution was extracted with ether, the ether layer was dried (Na_2CO_3) and evaporated, and the residue was distilled under vacuum to give 4-bromo-3-picoline (2.06 g), b.p. 104–107° at 60 mm. The picrate had m.p. 137–138°, undepressed on admixture with a sample prepared by method *a* above. Infrared spectrum of the free base (liquid film): 3 040 (m), 1 600 (w), 1 520 (s), 1 470 (m), 1 440 (m), 1 380 (m), 1 350 (s), 1 230 (s), 1 065 (s), 840 (s), 790 (s), 750 (s), 715 (w), 690 (s), and 670 (s) cm^{-1}.

1-(3′-Methyl-4′-pyridyl)cyclohexanol

A solution of *n*-butyllithium in ether was prepared from lithium (0.07 g), *n*-butyl bromide (4 ml), and dry ether (25 ml) at −62° to −74°. A solution of 4-bromo-3-picoline (0.860 g) in dry ether (5 ml) was added dropwise, with stirring, to the butyllithium solution over a period of 30 min, the temperature being maintained at −62° to −74°. Cyclohexanone (3.0 g) in dry ether was added dropwise over a period of ½ h, and then stirring was continued for another 3 h, during which time the reaction mixture was allowed to come to room temperature. The resulting mixture was poured onto crushed ice and extracted with ether. The dried ($MgSO_4$) ethereal layer was evaporated to give the alcohol (0.418 g), which was vacuum-distilled at 205–209° and 60 mm and then recrystallized from light petroleum (b.p. 60–80°). It was obtained as colorless prisms, m.p. 95°. Infrared spectrum (KBr disk): 3 180 (s), 1 590 (s), 1 255 (m), 1 210 (m), 1 165 (s), 1 125 (s), 1 065 (s), 965 (s), 822 (s), 805 (w), 755 (w), 745 (m), and 645 (s) cm^{-1}.

Anal. Found: C, 75.64; H, 8.81. $C_{12}H_{17}NO$ requires C, 75.35; H, 8.96.

4-Phenyl-3-picoline

1-(3′-Methyl-4′-pyridyl)cyclohexanol (0.20 g) was boiled under reflux with concentrated sulfuric acid (1.0 ml) and glacial acetic acid (3.0 ml) for 4 h, and the reaction mixture worked up as described for 5-phenyl-3-picoline. The product (0.054 g) had b.p. 195–198° at 60 mm. Infrared spectrum (liquid film): 3 340 (m, br), 1 585 (s), 1 475 (m), 830 (m), 805 (w), 760 (s), 735 (m), and 695 (s) cm^{-1}. Nuclear magnetic resonance spectrum (in CCl_4): τ 7.80 (3H, singlet, CH_3—Ar), 2.67 (5H, singlet, phenyl protons), 2.1 (1H, doublet, $J = 5$ c/s, C_5—H), and 1.4 (2H, multiplet caused by the superimposed singlet and doublet of C_2—H and C_6—H). The picrate (crystallized from benzene) had m.p. 168–169°.

Anal. Found: C, 54.07; H, 3.70. $C_{12}H_{11}N \cdot C_6H_3N_3O_7$ requires C, 54.27; H, 3.54.

General Method Used for the Phenylation of the Picolines and the Determination of the Isomer Ratios

A mixture of aniline (0.5 g) and concentrated hydrochloric acid (1 ml) was cooled to 0–5° and diazotized below 5° with a solution of sodium nitrite (0.42 g) in water (0.75 ml). The diazonium salt solution was slowly added over a period of 15 min to the picoline (100 ml), which was being stirred vigorously in a thermostat maintained at 40 ± 1°; the solution was then stirred at that temperature for a further 6 h. Sodium carbonate (5 g) was now added, the mixture was stirred at room temperature for 15 min and, after being allowed to stand for some time, was filtered into a distillation flask, and the solids were washed thoroughly with ether until free of picoline. The combined filtrates were concentrated carefully with a fractionating column to a volume of 20–30 ml. This was transferred quantitatively to a conical flask with the help of ether, the total volume being kept below 50 ml, and this solution was used directly for the quantitative analyses of the isomer ratios by gas–liquid chromatography.

For the quantitative analyses, the internal standard method (16) was used. The introduction of a known weight of internal standard in the final reaction mixture also permitted the yield of products to be determined. The authentic samples prepared as described above were all gas chromatographically pure. The conditions for the gas–liquid chromatographic analyses are given in each individual case.

Phenylation of 3-Picoline

The diazonium salt solution, prepared as described above, was added to 3-picoline (100 ml) at 40 ± 1° and worked up as usual. The reaction mixture was best resolved on a 5 ft × ¼ inch column packed with asphalt (15% w/w) on Chromosorb W (80–100 mesh) and operated at 220° and a helium inlet pressure of 40 p.s.i. (flow rate 75 ml/min). Under these conditions, four peaks were well resolved and had retention times of 24.5, 28.5, 39.5, and 45.0 min, respectively. These correspond to 2-phenyl-3-picoline, 4-phenyl-3-picoline, 6-phenyl-3-picoline, and 5-phenyl-3-picoline, respectively, and were identified by collecting samples corresponding to the individual peaks and comparing their infrared spectra with those of authentic samples. 2-Phenyl-3-picoline and 6-phenyl-3-picoline were available from a previous study (17). No 3-benzylpyridine (retention time 12.5 min) could be detected in the reaction mixture. The thermal detector responses of the four isomeric phenylpicolines were found to be the same, so that the relative areas under the chromatographic peaks could be used directly in the determination of the isomer ratios. 2-Methylbiphenyl was used as the internal standard. The percentage composition thus obtained (average of two runs in triplicate) was: 2-phenyl-, 43.3 ± 0.5%; 4-phenyl-, 28.7 ± 0.6%; 5-phenyl-, 6.9 ± 0.8%; and 6-phenyl-3-picoline, 21.1 ± 0.5%.

Phenylation of 4-Picoline

The reaction mixture was best resolved on a 6 ft × ¼ inch column packed with precipitated asphalt (25% by weight) on Chromosorb W (60–80 mesh) and operated at 175° and a helium inlet pressure of 40 p.s.i. (flow rate 80 ml/min). Under these conditions 3-phenyl-4-picoline had a retention time of 19.3 min and 2-phenyl-4-picoline a retention time of 27.4 min. Only two peaks were observed. Coumarin (retention time 22.2 min) was used as the internal standard. The compound giving rise to the peak corresponding in retention time to 2-phenyl-4-picoline was collected and found to be identical (melting point and infrared spectrum) with a sample prepared from phenyllithium and 4-picoline (18). The compound giving rise to the peak corresponding to 3-phenyl-4-picoline was collected and gave a picrate, m.p. 145°, undepressed on admixture with an authentic sample of the picrate of this base kindly supplied by Dr. J. N. Chatterjee (19). Infrared spectrum of the free base (liquid film): 1 610 (s), 1 475 (m), 1 455 (m), 1 415 (m), 1 225 (m), 1 015 (s), 830 (s), 765 (s), 730 (w), and 700 (s) cm^{-1}.

The molar thermal responses of the two isomers were different, so that the internal standard had to be

introduced in all the samples being analyzed. The percentage composition thus obtained (two runs in triplicate) was: 2-phenyl-, 44.9 ± 1.0%; and 3-phenyl-4-picoline, 55.1 ± 0.6%.

Determination of $^{3\text{-Pic}}_{C_6H_6}K$ *for the Phenylation of 3-Picoline*

(i) With a Molar Ratio of 3-Picoline to Benzene of 4:1

The ratio of aniline to total solvent was 1:200.

The diazonium salt solution from aniline (0.5 g), concentrated hydrochloric acid (1.0 ml), sodium nitrite (0.42 g), and water (0.7 ml) was added over a period of 15 min, with vigorous stirring, to a mixture of 3-picoline (83.0 ml) and benzene (19.0 ml) maintained at 40 ± 1° in a thermostat. The reaction mixture was stirred for a further 6 h and then worked up as described in the determination of the isomer ratios. It was analyzed by gas–liquid chromatography on a 6 ft × ¼ inch column packed with precipitated asphalt (15% w/w) on Chromosorb W (80–100 mesh) and operated at 220° and a helium inlet pressure of 40 p.s.i. Under these conditions biphenyl had a retention time of 8.3 min. Advantage was taken here of the fact that the phenyl-3-picolines have the same thermal detector response, so that no special calibrations were necessary. 2-Bromobiphenyl was used as the internal standard. The mean of the results of three runs carried out in duplicate gave $^{3\text{-Pic}}_{C_6H_6}K = 1.39 \pm 0.05$.

(ii) With a Molar Ratio of 3-Picoline to Benzene of 6:1

The same proportions of amine to total solvent were used. In this way, $^{3\text{-Pic}}_{C_6H_6}K$ was found to be 1.40±0.06.

Determination of $^{4\text{-Pic}}_{C_6H_6}K$ *for the Phenylation of 4-Picoline*

The reaction was carried out as described above, but with 4- instead of 3-picoline. The mixtures were analyzed on a 6 ft × ¼ inch column packed with precipitated asphalt (25% w/w) on Chromosorb W and operated at 175° and a helium inlet pressure of 40 p.s.i. (flow rate 80 ml/min). Under these conditions biphenyl had a retention time of 8.3 min, and 2- and 3-phenyl-4-picolines retention times of 22.6 and 16.4 min, respectively. Coumarin was used as the internal standard. The average of the results of three runs carried out in duplicate gave $^{4\text{-Pic}}_{C_6H_6}K = 1.39 \pm 0.1$.

DISCUSSION

Since the reaction mixtures were homogeneous in all cases, the argument sometimes levelled (20) against the suitability of the Gomberg–Hey reaction for quantitative work that, with the usual aromatic solvents, the reaction is a heterogeneous one does not apply. Selective solvation was not important within the range of solvent ratios used. The validity of isomer ratios obtained in the Gomberg–Hey arylation has already been discussed (1), and the conclusion was reached that the σ-complexes formed are not selectively removed by dimerization or disproportionation. No high-boiling products could be isolated in the reactions with the picolines. In view of the work-up and analytic procedure used the errors in the quantitative estimations are small and the results are reproducible within ±2% (in most cases much better than this).

The averaged proportions of isomeric phenylpicolines are given in Table I, which also includes the data for the phenylation of pyridine (1). The values of the total rate ratios

TABLE I

Averaged percentage ratios of phenylated pyridines formed at 40 ± 1° and total rate ratios

Compound	Isomer distribution					$^{XC_5H_4N}_{C_6H_6}K$
	2-	3-	4-	5-	6-	
Pyridine (1)	52.4	29.6	18.0	—	—	1.14
3-Picoline	43.3	—	28.7	6.9	21.1	1.39
4-Picoline	44.9	55.1	—	—	—	1.39

$^{XC_5H_4N}_{C_6H_6}K$ relative to benzene are also given (corrected for the statistical relative amounts of benzene and XC_5H_4N used in the competitive reactions). A previous study (1) had shown that the most convenient molar ratio of pyridine to benzene to use in the competitive runs was 4:1. Under such conditions the mixtures were homogeneous and no selective solvation of the diazonium salt or covalent diazo compound was occurring. This was also found to be the case here in the competitive runs with the picolines and benzene. Increasing the molar ratio of 3-picoline to benzene to 6:1 had no effect upon the total rate ratio.

The results indicate that the 3- and 4-methyl groups activate the pyridine nucleus slightly (as expected) towards attack by phenyl radicals, and to the same extent (${}^{Plc}_{Pyr}K$ = 1.22). This is about the same degree of activation as is imparted by a methyl substituent onto a benzene ring (${}^{C_6H_5CH_3}_{C_6H_6}K$ = 1.23) (21). (See, however, the more recent results with triphenylbismuth as the source of phenyl radicals to substitute toluene, in which ${}^{CH_3}_{H}K$ was found to be 1.99 on the assumption that there is no side-chain attack (9). This value appears to be too high. Abramovitch and Saha (22), using benzenediazonium tetrafluoroborate and pyridine as the source of phenyl radicals, obtained a value of 1.20 for this total rate ratio.)

The most abundant isomers obtained in the phenylation of the picolines are those in which the phenyl group enters ortho to the methyl group, which is consistent with the orientation observed in previous homolytic substitutions of 3- and 4-alkylpyridines (3, 5, 7). The effect of the methyl group may be seen more clearly from a consideration of the partial rate factors for the phenylations. These are given in Table II together with the data for pyridine itself (1).

TABLE II

Partial rate factors for phenylation at 40 ± 1°

	Partial rate factors				
Compound	F_2	F_3	F_4	F_5	F_6
Pyridine (1)	1.83	1.00	1.18	—	—
3-Picoline	3.5	—	2.37	0.57	1.74
4-Picoline	1.87	2.29	—	—	—

If the principle of additivity (23) is presumed to hold in these substitutions, then the partial rate factors for the various positions in the picolines can be calculated from the partial rate factors for the phenylation of pyridine and of toluene. The data for toluene are, as mentioned above, not definitive. The latest values of the isomer ratios as obtained from the phenylation with triphenylbismuth (9) have been confirmed in our laboratories with benzoyl peroxide as the source of phenyl radicals, the analysis being carried out by gas–liquid chromatography, using the internal standard technique. The isomer ratio so obtained is: *o*-, 57%; *m*-, 25%; and *p*-, 18% (24). If the values for the partial rate factors originally given by Hey *et al.* (21) are used in conjunction with our data for pyridine, the values calculated for 3-picoline are: F_2 = 4.58, F_4 = 2.95, F_5 = 0.71, and F_6 = 1.83; and those for 4-picoline are: F_2 = 1.30 and F_3 = 2.50. If the partial rate factors based on ${}^{C_6H_5CH_3}_{C_6H_6}K$ = 1.99 (9) are used, then the calculated values for 3-picoline are: F_2 = 6.22, F_4 = 4.0, F_5 = 1.6, and F_6 = 3.48; and those for 4-picoline are: F_2 = 2.93 and F_3 = 3.4. These values are obviously much too high and confirm that the total rate ratio for toluene is probably close to 1.23. Using this figure and our data for the isomer ratios (24) leads to the following predicted values for 3-picoline: F_2 = 3.85, F_4 = 2.47, F_5 = 0.92, and F_6 = 2.43; and for 4-picoline: F_2 = 1.69 and F_3 = 2.10. Except for F_5 in 3-picoline (and perhaps F_6 as well), these agree reasonably well with the experimentally found values. This additivity of the substituent effects supports the assumption that formation of the σ-complexes is the rate-determining step in such substitution reactions.

The apparent deactivation of C_5 in 3-picoline towards attack by phenyl radicals is unexpected. The proportion of 5-isomer obtained in the methylation of 3-*n*-butylpyridine was similarly low (2%) (7), but partial rate factors are not available in this case. A similar, though lesser, deactivation of the meta position in toluene has been reported (F_m = 0.71 (21), F_m = 0.76 (22)) but the data from the reaction with triphenylbismuth give F_m = 1.6

(9). Again, using our data for the isomer ratio (24) and ${}^{C_6H_5CH_3}_{C_6H_6}K = 1.23$, one gets $F_m = 0.92$, which is close enough to 1 to be well within the experimental error. The still lower yield of 3-*n*-butyl-5-methylpyridine obtained in the methylation of 3-*n*-butylpyridine is readily explained on the basis that methyl radicals are more nucleophilic than phenyl radicals (20), so that a deactivation of the pyridine β-position is to be expected towards "nucleophilic" attack. The low value of F_5 found for the phenylation of 3-picoline might be due to a systematic experimental error and could be without real significance. This seems to be rather unlikely at the moment. Another possibility worth considering is that phenyl radicals have a slight nucleophilic character. All substituents activate the benzene nucleus towards attack by phenyl radicals, barring steric hindrance (25). This is probably due to the fact that substituents, whether electron attracting or donating, can delocalize a single electron in the σ-complexes obtained by attack at the ortho and para positions. When the substrate is pyridine, attack by the radical at the α- and γ-positions will eventually lead to σ-complexes in which one of the contributing structures has the odd electron on the nitrogen atom. No further delocalization is, however, possible. It has tentatively been suggested (2) that, if anything, the phenyl radical has to be slightly nucleophilic to account for the slightly greater reactivity of pyridine compared with that of benzene. Although this would explain the deactivation of C_5 in 3-picoline, it would leave other data unaccounted for, e.g. F_m for nitrobenzene is reported to be 0.86 (25). Since many of these values are very close to 1, however, the slight variations around this figure may, in some cases, be within the limits of experimental error and not be significant at all. In any event, no firm statement is warranted at this time.

The formation of the 3-phenyl derivative as the main product in the phenylation of 4-picoline is another example of a case in which the 3-isomer is the predominant one formed. Other examples are the *o*-nitrophenylation (1) and the *o*-bromophenylation (2) of pyridine.

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