

#### 404. *Aromatic Substitution. Part III.<sup>1,2</sup> Reaction of Pyridine with ortho-Substituted Phenyl Radicals, and the Influence of Oxygen upon Isomer Ratios in the Gomberg-Hey Reaction.*

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Relative rates of arylation of pyridine with *o*-tolyl and *o*-nitrophenyl radicals produced by the Gomberg-Hey reaction have been measured by means of competitive experiments. The ratios of isomers, and total and partial rate factors have been compared with those obtained with the corresponding *para*-substituted aryl radicals and the unsubstituted phenyl radical. *o*-Tolyl radicals gave less  $\alpha$ -isomer, and *o*-nitrophenyl radicals more  $\alpha$ -isomer than expected. A new type of "*ortho*-effect" is suggested to rationalise these results. As expected, tolyl radicals are nucleophilic and nitrophenyl radicals are electrophilic when compared with the unsubstituted phenyl radical. The ratios of isomers formed were relatively unaffected (within experimental error) by the presence of oxygen. The significance of this observation in terms of a possible mechanism for the reaction is discussed.

THIS Paper reports a study of the orientation of the entering substituent when pyridine is attacked by *ortho*-substituted phenyl radicals, and attempts to unravel factors which determine the observed isomer ratios. The latter can only be used meaningfully if they reflect the reactivities of the various nuclear positions in pyridine towards free-radical attack. This is shown to be true for the Gomberg-Hey reaction.

There are conflicting opinions concerning the effects of the *ortho*-substituents on the mechanism and orientation in the reactions of aromatic compounds with *ortho*-substituted phenyl radicals, and in a number of instances apparently anomalous products have been obtained in preparative reactions (for summary see Hey, Moulden, and Williams<sup>3</sup>). Hey and Walker<sup>4</sup> isolated methyl benzoate and two isomeric methyl *o*-pyridylbenzoates from the reaction of *o*-methoxycarbonylbenzoyl peroxide and pyridine. This reaction was later re-investigated by Hey and Williams<sup>5</sup> who isolated only methyl *o*-3-pyridylbenzoate from the reaction of diazotised methyl anthranilate with pyridine. Molecular-orbital calculations predict that when pyridine is substituted by a free-radical the proportion of isomers formed will be in the order  $\alpha > \beta > \gamma$ ,<sup>6</sup> and this order has been observed in a number of reactions, *e.g.*, the phenylation of pyridine.<sup>7</sup> On the other hand, preparative *o*-nitrophenylation of pyridine<sup>8</sup> gave the three isomeric *o*-nitrophenylpyridines in the ratio  $\beta : \alpha : \gamma :: 52 : 45 : 3$ . No abnormality was noted, however, in the reactions of diazotised *p*- and *m*-nitroanilines with pyridine. Hey, Moulden, and Williams<sup>3</sup> recently studied quantitatively the relative rates of arylation of nitrobenzene, chlorobenzene, and toluene with *o*-bromo- and *o*-nitrophenyl radicals and determined the isomer distributions in some of these reactions. Toluene was found to be less reactive towards *o*-nitrophenylation than towards *p*-nitrophenylation, contrary to expectations based on the relative electrophilicity of these two radicals. It was assumed that this was due to some steric hindrance to the attachment of the *o*-substituted radical at the *ortho*-positions of toluene leading to a reduction of the total reactivity of that molecule (isomer ratios were not reported in this case, however). Furthermore, no side-chain attack of toluene was observed with *p*-nitrophenyl radicals whereas 11% side-chain attack took place with *o*-nitrophenyl radicals. A number of possible explanations were considered, including a

<sup>1</sup> Part II, Abramovitch, Ahmed, and Giam, *Canad. J. Chem.*, 1963, **41**, 1752.

<sup>2</sup> Abramovitch and Saha, *Tetrahedron Letters*, 1963, 301.

<sup>3</sup> Hey, Moulden, and Williams, *J.*, 1960, 3769.

<sup>4</sup> Hey and Walker, *J.*, 1948, 2213.

<sup>5</sup> Hey and Williams, *J.*, 1951, 1527.

<sup>6</sup> Yvan, *Compt. rend.*, 1949, **229**, 622; Brown, *J.*, 1956, 272.

<sup>7</sup> Hey, Stirling, and Williams, *J.*, 1955, 3963.

<sup>8</sup> Haworth, Heilbron, and Hey, *J.*, 1940, 349.

different type of steric influence, namely, an interaction between an *ortho*-substituent present in the radical and the  $\pi$ -electrons of the nucleus of the substrate molecule during the formation of the transition state. In contrast to this, from a study of the isomer distributions in the arylation of *o*- and *m*-dichlorobenzene with phenyl, *o*- and *p*-chlorophenyl, *o*-bromophenyl, and *o*-tolyl radicals Weingarten<sup>9</sup> concluded that steric effects were relatively unimportant in the Gomberg–Hey reaction, while *ortho*-halogen substitution may give rise to unfavourable dipolar repulsions in the transition state. He suggested further that the attacking radical was almost perpendicular to the plane of the substrate in the transition state, forming a long “ $\pi$ -like” bond.

It therefore appeared that the nature of “*ortho*-effects” in the substitution of aromatic compounds by *ortho*-substituted phenyl radicals is still in question, and it was decided to investigate the *o*-nitrophenylation and *o*-tolylation of pyridine and to compare the results with those obtained in the substitutions by the corresponding *para*-substituted aryl radicals and the unsubstituted phenyl radical. The choice of pyridine as the aromatic substrate was based on two considerations: (i) pyridine, behaving in many ways as a monosubstituted benzene derivative, would be free of most of the steric effects due to the substituents present in the examples previously studied<sup>3,9</sup> and, (ii) except for phenylation the other radical substitutions of pyridine have only been studied from a qualitative point of view and it was necessary to put them on a quantitative footing before the implication of such results as those mentioned above<sup>4,8</sup> were examined.

The concept that valuable information about the relative reactivities of different nuclear positions may be derived from a consideration of partial rate factors in homolytic aromatic substitutions has been questioned<sup>10–12</sup> particularly when peroxides are used as the source of radicals, mainly on the basis of certain product isotope effects<sup>10</sup> and the finding of products formed by dimerisation<sup>13</sup> and disproportionation<sup>14</sup> under some reaction conditions. It has been suggested that, for such homolytic arylations with diaryl peroxides, the observed isomer distributions may not truly reflect whatever discrimination between positions there is in a monosubstituted benzene in the radical-addition step, because of the possibility that the intermediate isomeric arylcyclohexadienyl radicals formed might undergo side-reactions at different rates. Eberhardt and Eliel<sup>15</sup> have suggested that if this is the case the determination of isomer ratios may give a truer picture of the reactivities of the different positions towards aryl radicals if oxygen were passed through the reaction mixtures. This point was investigated in the present work. Since this investigation was completed Morrison and his co-workers<sup>16</sup> have found that oxygen has no effect upon the isomer distribution and relative reactivities in the phenylation by benzoyl peroxide of four substituted benzenes, though in some cases biaryl yields were increased as much as three-fold in the presence of oxygen. Eliel, Eberhardt, Simamura, and Meyerson<sup>17</sup> have shown, furthermore, that dihydrobiaryls are not formed in either concentrated or dilute solution during the decomposition of *N*-nitrosoacetanilide in benzene, and that there is no appreciable apparent isotope effect in this reaction.

A number of reference compounds had to be prepared. 2-Methyl-1-3'-pyridylcyclohexanol was not dehydrated by distillation at atmospheric pressure or by boiling with catalytic amount of alumina (cf. the behaviour of 3'-pyridylcyclohexan-1-ol<sup>18</sup>), but gave

<sup>9</sup> Weingarten, *J. Org. Chem.*, 1961, **26**, 730.

<sup>10</sup> Eliel, Meyerson, Welvert, and Wilen, *J. Amer. Chem. Soc.*, 1960, **82**, 2936.

<sup>11</sup> DeTar, Abstracts 17th National Organic Chem. Symp., Amer. Chem. Soc., Bloomington, Ind., 1961, pp. 64–70.

<sup>12</sup> DeTar, *J. Amer. Chem. Soc.*, 1961, **83**, 1014.

<sup>13</sup> Lynch and Pausacker, *Austral. J. Chem.*, 1957, **10**, 40; Pausacker, *ibid.*, p. 49; Lynch and Pausacker, *ibid.*, p. 165.

<sup>14</sup> DeTar and Long, *J. Amer. Chem. Soc.*, 1958, **80**, 4742.

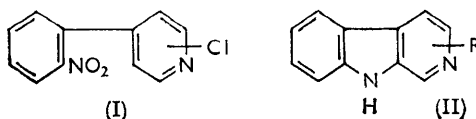
<sup>15</sup> Eberhardt and Eliel, *J. Org. Chem.*, 1962, **27**, 2289.

<sup>16</sup> Morrison, Cazes, Samkoff, and Howe, *J. Amer. Chem. Soc.*, 1962, **84**, 4152.

<sup>17</sup> Eliel, Eberhardt, Simamura, and Meyerson, *Tetrahedron Letters*, 1962, 749.

<sup>18</sup> Wiley, Callahan, Jarboe, Nielsen, and Wakefield, *J. Org. Chem.*, 1960, **25**, 366.

the required 3-*o*-tolylpyridine when heated with glacial acetic acid containing concentrated sulphuric acid. The other tertiary alcohols prepared here behaved similarly. Pure



4-*o*-nitrophenylpyridine could not be obtained from diazotised *o*-nitroaniline and pyridine followed by fractional crystallisation of the picrates. An attempt to synthesise it by the Ullmann condensation of 4-chloropyridine 1-oxide with an excess of *o*-bromonitrobenzene, gave, presumably, 4-*o*-nitrophenylpyridine 1-oxide contaminated with starting material and basic by-products. When this crude product was treated with phosphorus trichloride in dry chloroform, a basic compound,  $C_{11}H_7N_2O_2Cl$ , containing a nitro-group but different from the known<sup>19</sup> 4-*o*-nitrophenylpyridine, could be isolated. This is clearly 2-(or 3)-chloro-4-*o*-nitrophenylpyridine (I), resulting from the deoxygenation and nuclear halogenation of 4-*o*-nitrophenylpyridine 1-oxide. Taylor and Driscoll<sup>20</sup> found that 3-nitropyridine 1-oxide gave a mixture of 2-chloro- and 6-chloro-3-nitropyridine. The ultraviolet absorption spectrum of (I) was very similar to those of 2- and 3-*o*-nitrophenylpyridine (Table I). The suggested structure was further supported by the conversion of the com-

TABLE I.

Ultraviolet absorption spectra of some *o*-nitrophenylpyridines in 95% ethanol.

	2-Compound	3-Compound	(I)
$\lambda_{max}$ (m $\mu$ ) .....	202, 222·8, 261	201, 224·7, 261	201, 224·7sh, 261
$10^{-3}\epsilon$ .....	25·1, 21·8, 10·9	56·9, 26·9, 11·9	38·0, 21·0, 8·5

pound into a chloro- $\beta$ -carboline (II; R = Cl) with ferrous oxalate.<sup>21</sup> The position of the chlorine atom in (I) has not been determined conclusively. The n.m.r. spectrum of the compound exhibits a two-proton peak (triplet) centred at 516 c/sec., characteristic of pyridine  $\alpha$ -protons.<sup>22</sup> From this it would appear that the chlorine is at C-3 of the pyridine ring so that (II) would then be 4-chloro- $\beta$ -carboline. The n.m.r. spectrum of a very dilute solution of (II) in carbon disulphide did not exhibit a band at around 555 c./sec., however, whereas  $\beta$ -carboline does, which band has been assigned to  $C_1$ -H.<sup>22b</sup> This would indicate that (II) is 1-chloro- $\beta$ -carboline and (I) the 2-chloro-derivative. This conflicting evidence remains to be resolved as sufficient quantities of (I) and (II) were not available to permit further investigation. Attempts to reduce the 1-oxide group in crude 4-*o*-nitrophenylpyridine 1-oxide selectively were unsuccessful. 4-*o*-Nitrophenylpyridine was prepared by a modification of the method of Forsyth and Pyman<sup>19</sup> and its structure proved by converting it into  $\beta$ -carboline (II; R = H) with ferrous oxalate.

Isomer ratios were determined by adding a solution of the relevant diazonium salt in the minimum amount of water to an excess of pyridine at 40°. Under these conditions the reaction mixture remained homogeneous at all times. The concentrated solution was analysed directly by g.l.c. To study the effect of oxygen on the isomer ratios runs were carried out with phenyl, *o*-tolyl, and *p*-tolyl radicals (a) under oxygen-free nitrogen, (b) in air, and (c) by bubbling oxygen through the reaction mixtures.

The relative rates of arylation of pyridine and benzene with phenyl, *o*- and *p*-tolyl, and *o*- and *p*-nitrophenyl radicals were determined by using a modification of the competitive technique devised by Augood, Hey, and Williams.<sup>23</sup> When benzenediazonium

<sup>19</sup> Forsyth and Pyman, *J.*, 1926, 2919.

<sup>20</sup> Taylor and Driscoll, *J. Org. Chem.*, 1960, **25**, 1716.

<sup>21</sup> Abramovitch and Adams, *Canad. J. Chem.*, 1961, **39**, 2516.

<sup>22</sup> (a) Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959, p. 64; Abramovitch, Giam, and Notation, *Canad. J. Chem.*, 1960, **38**, 761; (b) Abramovitch and Spenser, *Canad. J. Chem.*, 1964, **42**, 954.

<sup>23</sup> Augood, Hey, and Williams, *J.*, 1952, 2094.

chloride solution was added to a large excess of an equimolar mixture of pyridine (Py) and benzene (Benz) the values of  $\frac{Py}{Benz}K$  were too high and not reproducible. When the proportion of pyridine in the mixture was increased the value of  $\frac{Py}{Benz}K$  fell from around 2.8 to 1.6, as compared with the value of 1.04 reported for the phenylation by using benzoyl peroxide as the source of radicals.<sup>23</sup> A minimum value of  $\frac{Py}{Benz}K = 1.14$  was obtained with the ratio pyridine : benzene = 4 : 1, and this value remained unchanged with further increases in the proportion of pyridine in the reaction mixture. The high value of the total rate ratio at low concentrations of pyridine may be explained if it is appreciated that under such conditions the reaction mixture is heterogeneous to some extent, resulting in the reaction of pyridine with the diazoate both in the water and in the non-aqueous layer. At higher concentrations of pyridine the solutions are homogeneous. That selective solvation is no longer important under the conditions finally selected is indicated by the fact that a constant value for the total rate ratio is attained and is unaffected by further additions of pyridine. The slightly lower value of  $\frac{Py}{Benz}K$  reported for the phenylations by benzoyl peroxide<sup>23</sup> may be insignificant, or might reflect to a very small extent the tendency for pyridine to form the *N*-oxide under the oxidising condition.<sup>24</sup>

### EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were measured on a Perkin-Elmer model 21 spectrometer equipped with sodium chloride optics, u.v. absorption spectra on a Cary model 14 recording spectrophotometer, and n.m.r. spectra on a Varian A60 instrument, carbon tetrachloride solutions of the compounds being used, with tetramethylsilane as the internal standard. The oscillator frequency was 60 Mc./sec.

*Reagents.*—AnalaR thiophen-free benzene was dried, distilled, and kept over sodium wire. Pyridine (Reilly Tar and Chemical Co., 2° grade) was dried over potassium hydroxide pellets and distilled; the fraction, b. p. 114—115°/760 mm. was collected and kept over potassium hydroxide pellets. Aniline, *o*- and *p*-toluidine, and *o*- and *p*-nitroaniline were purified by standard procedures and had the boiling points or melting points reported in the literature.

2-Phenylpyridine was prepared from pyridine and phenyl-lithium.<sup>25</sup> 3-Phenylpyridine was prepared as described by Wiley *et al.*<sup>18</sup> while 4-phenylpyridine was prepared in large quantities from  $\alpha$ -methylstyrene, ammonium chloride, and formaldehyde,<sup>26</sup> followed by dehydrogenation of the tetrahydro-derivative. 2- and 3-*o*-nitrophenylpyridine and 2-, 3-, and 4-*p*-nitrophenylpyridine were prepared by the Gomberg-Hey reaction.<sup>8</sup>

2-*c*-Tolylpyridine was prepared in 43% yield by reaction of *o*-tolyl-lithium with pyridine in ether, followed by replacing the ether by toluene and heating under reflux at *ca.* 110°.<sup>27</sup> 2-*p*-Tolylpyridine (59.5% yield), b. p. 170—180°/20 mm. (picrate, m. p. 184.5—185.5°), was similarly prepared from *p*-tolyl-lithium and pyridine; it had infrared spectrum (liquid film) 1617w, 1595s, 1570m, 1520w, 1475s, 1440s, 1300m, 1187m, 1155w, 827m, 737s, 735m cm.<sup>-1</sup>. Cumper, Ginman, and Vogel<sup>28</sup> report b. p. 142°/10 mm. (picrate, m. p. 182.5—183.5°) for this compound.

2-Methyl-1-3'-pyridylcyclohexanol.—A solution of *n*-butyl-lithium (9.6 g.) in hexane (65 ml.) and ether (60 ml.) was stirred under dry nitrogen and cooled to between -62 and -74°. 3-Bromopyridine (20.0 g.) in dry ether (20 ml.) was added with stirring during 20 min. and stirring continued at -70° for 15 min. 2-Methylcyclohexanone (16.5 g.) was now added during 15 min. and stirring at -70° continued for 30 min. and for a further 3 hr. during which the temperature of the mixture was allowed to rise to room temperature. The brown solution was poured on ice and steam-distilled, the residue was extracted with ether, the organic layer was dried (MgSO<sub>4</sub>), the solvent was evaporated, and the residue was distilled to give 2-methyl-1-3'-pyridylcyclohexanol (17.0 g.), b. p. 110—115°/0.3 mm., m. p. 97—99°;  $\nu_{max}$ , (KBr disc)

<sup>24</sup> Pausacker, *Austral. J. Chem.*, 1958, **11**, 200.

<sup>25</sup> Evans and Allen, *Org. Synth., Coll. Vol. II*, 1943, 517.

<sup>26</sup> Schmidle and Mansfield, *J. Amer. Chem. Soc.*, 1956, **78**, 1702.

<sup>27</sup> Abramovitch, Thesis, London, 1953.

<sup>28</sup> Cumper, Ginman, and Vogel, *J.*, 1962, 4525.



3240s, 1595s, 1580m, 1265s, 910s, 900s, 810m, 805m, 790m, 710s  $\text{cm}^{-1}$ . The *picrate*, which separated from benzene and crystallised from ethanol, had m. p. 164.5–165° (Found: C, 51.4; H, 5.0.  $\text{C}_{12}\text{H}_{17}\text{NO}_7$  requires C, 51.4; H, 4.8%).

**3-o-Tolylpyridine.**—2-Methyl-1-3'-pyridylcyclohexanol (0.78 g.) in glacial acetic acid (5 ml.) and concentrated sulphuric acid (1 ml.) was boiled under reflux for 2.5 hr. Most of the acetic acid was distilled off, and the residue cooled and poured into water. The solution was made alkaline with 10% aqueous sodium hydroxide and extracted with ether. The dried ( $\text{MgSO}_4$ ) ether extract was evaporated and the residue distilled *in vacuo* to give 3-o-tolylpyridine (0.51 g.), b. p. 140–150°/20–25 mm.;  $\nu_{\text{max}}$  (liquid film) 1567m, 1475s, 1412s, 1190w, 1130m, 1005s, 815m, 805m, 755s, 712s  $\text{cm}^{-1}$ . The *picrate* (from benzene) had m. p. 169–169.5° (Found: C, 54.35; H, 3.5.  $\text{C}_{12}\text{H}_{11}\text{N}_2\text{O}_7$  requires C, 54.3; H, 3.5%).

**2-Methyl-1-4'-pyridylcyclohexanol.**—Prepared similarly to the 3'-pyridyl derivative, this *alcohol* (61% yield) had b. p. 170–190°/18–25 mm.;  $\nu_{\text{max}}$  (KBr disc) 3200s, 2900s, 1600s, 1000s, 970m, 810s, 800m  $\text{cm}^{-1}$ . The *picrate* (from benzene) had m. p. 163–164° (Found: C, 51.4; H, 4.9.  $\text{C}_{12}\text{H}_{17}\text{NO}_7$  requires C, 51.4; H, 4.8%).

**4-o-Tolylpyridine.**—The dehydration and dehydrogenation of 2-methyl-1-4'-pyridylcyclohexanol (2.0 g.) with glacial acetic acid (10 ml.) and concentrated sulphuric acid (2 ml.) gave 4-o-tolylpyridine (1.2 g.), b. p. 160–170°/20–25 mm.;  $\nu_{\text{max}}$  (liquid film) 1600s, 1545m, 825s, 800m, 757s, 742m, 720m  $\text{cm}^{-1}$ . The *picrate* (from benzene) had m. p. 173.5–174° (Found: C, 54.2; H, 3.6.  $\text{C}_{12}\text{H}_{11}\text{N}_2\text{O}_7$  requires C, 54.3; H, 3.5%).

**4-Methyl-1-3'-pyridylcyclohexanol.**—Prepared from 3-bromopyridine and 4-methylcyclohexanone the *alcohol* (88%) had b. p. 170–190°/20–25 mm., m. p. 81–82.5° [from light petroleum (b. p. 40–60°)];  $\nu_{\text{max}}$  (KBr disc) 3220s, 1595m, 1582m, 970m, 927s, 905s, 810s, 710s  $\text{cm}^{-1}$ . The *picrate* (from benzene) had m. p. 152–153° (Found: C, 51.6; H, 4.9.  $\text{C}_{12}\text{H}_{17}\text{NO}_7$  requires C, 51.4; H, 4.8%).

**3-p-Tolylpyridine.**—Dehydration and dehydrogenation of 4-methyl-1-3'-pyridylcyclohexanol (2.7 g.) with a mixture of glacial acetic acid and concentrated sulphuric acid gave 3-p-tolylpyridine (1.8 g., 76%), b. p. 170–180°/20–25 mm.;  $\nu_{\text{max}}$  (liquid film) 1585m, 1520m, 1000s, 825m, 795s, 705s  $\text{cm}^{-1}$ . The *picrate* (from benzene) had m. p. 175–176° (Found: C, 54.3; H, 3.9.  $\text{C}_{12}\text{H}_{11}\text{N}_2\text{O}_7$  requires C, 54.3; H, 3.5%).

**4-Methyl-1-4'-pyridylcyclohexanol.**—Prepared in 54% yield from 4-bromopyridine and 4-methylcyclohexanone, this had b. p. 175–190°/20 mm., m. p. 92–94°;  $\nu_{\text{max}}$  (KBr disc) 3200s, 1600s, 1555m, 1000s, 810s  $\text{cm}^{-1}$ . The *picrate* separated from benzene and on recrystallisation from ethanol had m. p. 212.5–213° (Found: C, 51.5; H, 4.9.  $\text{C}_{12}\text{H}_{17}\text{NO}_7$  requires C, 51.4; H, 4.8%).

**4-p-Tolylpyridine.**—This was obtained in 80% yield from the above *alcohol*, and had b. p. 95–105°/0.1 mm. Recrystallisation from heptane gave a product, m. p. 89.5–90.5°. The *picrate* (from benzene) had m. p. 200–201°. Schmidle, Locke, and Mansfield<sup>29</sup> report m. p. 90–91° for this compound and m. p. 199–201° for its *picrate*.

**4-o-Nitrophenylpyridine.**—4-Phenylpyridine (12 g.) was nitrated with fuming nitric acid in sulphuric acid as described by Forsyth and Pyman<sup>19</sup> and the mixed nitrophenylpyridines obtained as a dark brown oil (14.2 g.). The mixture was resolved by g.l.c. on a 2.5 ft.  $\times$   $\frac{1}{4}$  in. column of 15% Apiezon N on Fluoropak at 220° with a helium inlet pressure of 30 p.s.i. The chromatogram showed one completely resolved peak (retention time 8 min.) and another peak (retention time 18 min.) with a shoulder (retention time 17 min.). The compound giving rise to the first peak was shown to be 4-o-nitrophenylpyridine.

**$\beta$ -Carboline.**—4-o-Nitrophenylpyridine (37 mg.) (obtained as above) was mixed with anhydrous ferrous oxalate (100 mg.) and granulated lead (370 mg.), and the mixture heated under air-condenser at 270–290° for 40 min., allowed to cool, and extracted with acetone, and the extract filtered and evaporated. The residue was chromatographed on a short column of alumina (Peter Spence type H) and eluted with benzene-ether (1 : 1 v/v). Woolly crystals of  $\beta$ -carboline, m. p. and mixed m. p.<sup>30</sup> 195°, were thus obtained.

**Reaction of 4-Chloropyridine 1-Oxide with o-Bromonitrobenzene.**—A stirred mixture of 4-chloropyridine 1-oxide<sup>31</sup> (2 g.), o-bromonitrobenzene (9.3 g.), and ethylbenzene (30 ml.) was boiled. Copper powder (12 g.) was added during 2 hr. and stirring and boiling maintained for a

<sup>29</sup> Schmidle, Locke, and Mansfield, *J. Org. Chem.*, 1956, **21**, 1194.

<sup>30</sup> Abramovitch and Adams, *Canad. J. Chem.*, 1962, **40**, 864.

<sup>31</sup> Ochiai, *J. Org. Chem.*, 1953, **18**, 534.

further hour. The ethylbenzene was distilled off and the residue heated at 160–170° for 1 hr., and then cooled to room temperature, and the solid mass extracted (Soxhlet) with chloroform. The chloroform solution was extracted with 10% hydrochloric acid, and the acidic solution made alkaline with ammonia and extracted repeatedly with chloroform. The dried ( $K_2CO_3$ ) chloroform solution was evaporated and the residue treated with phosphorus trichloride (20 ml.) in dry chloroform (20 ml.) at 0–10° for 1 hr. The solution was poured on crushed ice, the chloroform layer was extracted with dilute hydrochloric acid, and the combined acid extracts and aqueous layer were made alkaline with 10% sodium hydroxide solution and extracted with chloroform. The dried ( $MgSO_4$ ) extract was evaporated and the residue distilled to give somewhat impure 2-(or 3)-chloro-4-o-nitrophenylpyridine, m. p. 72° (from ether) (Found: C, 55.6; H, 3.4.  $C_{11}H_7ClN_2O_2$  requires C, 56.3; H, 3.0%);  $\nu_{max}$  (KBr disc) 1560s, 1525s, 1350s, 885m, 860m, 830m, 805m, 778s, 763m, 735s, 710m, 700s, 670w  $cm^{-1}$ . The *picrate* (from benzene) had m. p. 146–146.5° (Found: C, 44.2; H, 2.3.  $C_{11}H_7ClN_2O_2 \cdot C_6H_3N_3O_7$  requires C, 44.1; H, 2.2%).

*Cyclisation of x-Chloro-4-o-nitrophenylpyridine with Ferrous Oxalate.*—The Ullmann reaction product (0.171 g.), anhydrous ferrous oxalate (0.372 g.), and granulated lead (1.71 g.) were heated under air-condenser at 275–295° for 40 min., cooled to room temperature, and extracted with chloroform. Evaporation to dryness gave a wax (0.105 g.) which, on crystallisation from benzene gave x-chloro- $\beta$ -carboline, m. p. 195° (Found: C, 65.0; H, 3.6; N, 14.2.  $C_{11}H_7ClN_2$  requires C, 65.2; H, 3.5; N, 13.8%);  $\lambda_{max}$ , 227, 266, 274, 330  $m\mu$ ;  $\nu_{max}$  (KBr disc) 1640s, 1525m, 865m, 800s, 740s, 700s  $cm^{-1}$ .

*General Procedure for Arylation of Pyridine.*—A solution of the aromatic amine (0.5 g.) in concentrated hydrochloric acid (1.0 ml.) was cooled to 0° and treated with sodium nitrite (0.42 g.) in water (0.75 ml.), the temperature being kept below 5°. The solution was added slowly with vigorous stirring during 15 min. to pyridine (100 ml.) maintained at  $40 \pm 0.1^\circ$ , (a) the mixture being kept open to the atmosphere, or (b) while oxygen was bubbled through the mixture at the rate of 10–15 ml./min., or (c) in an oxygen-free nitrogen atmosphere. Stirring of the mixture was continued for 6 hr. at this temperature, after which sodium carbonate (5 g.) was added, the mixture was stirred for 15 min., and then kept at room temperature for 24 hr. The suspension was filtered, the solids washed thoroughly with ether, and the combined filtrates distilled carefully through a fractionating column until a residue of about 20–30 ml. was left. This was transferred quantitatively to a weighed 50-ml. flask, ether being used to wash the distillation flask. The weight of the mixture was determined. This mixture was then used for the analysis of the isomer ratio and the determination of the total yield of arylpyridines. The validity of all analyses was always checked by similar analyses of synthetic mixtures of comparable composition.

*Determination of Ratios of Isomers formed in the Phenylation of Pyridine.*—The reaction mixture was best resolved on an 8 ft.  $\times \frac{1}{4}$  in. column packed with ethylene glycol succinate (10%) on Chromosorb W. The column temperature was 155° and the helium inlet pressure 30 lb./sq. in. (flow rate 43 ml./min.). Three peaks corresponding to 2-, 3-, and 4-phenylpyridine (retention times and infrared spectra) with retention times of 35.75, 41.25, and 45.0 min., respectively, were observed. Calibration curves indicated that the molar detector (thermal conductivity) responses of the three isomers were identical. The results are summarised in Table 2.

TABLE 2.

Composition (%) of mixtures of phenylpyridines, determined by g.l.c.

- (a) Obtained in presence of air: 2-, 53.6; 3-, 29.3; 4-, 17.1 (mean of 3 experiments).
- (b) Obtained by passing oxygen through the reaction mixture: 2-, 52.2; 3-, 29.8; 4-, 18.0 (mean of 3 experiments).
- (c) Obtained by carrying out the reaction under nitrogen: 2-, 51.3; 3-, 29.8; 4-, 19.0 (mean of 2 experiments).

*Determination of Overall Yield of Phenylpyridines.*—This was determined for the three experiments of Table 2(a) by g.l.c. on a 3 ft.  $\times \frac{1}{4}$  in. column packed with Apiezon N (15% by weight) on Chromosorb W, a column temperature of 160° and a helium flow rate of 120 ml./min. being used. Under these conditions the three phenylpyridines had the same retention time (7.4 min.), so that only one peak was obtained. A calibration curve (of peak area against

amount of phenylpyridine) was prepared with a standard solution of a synthetic mixture of the three isomers having the same composition as that found in the isomer-ratio determinations. A known weight of the mixture was then chromatographed, and the total amount of phenylpyridines present in the reaction mixture could then be calculated. The yields of phenylpyridines obtained in this way accounted for 70–75% of the aniline used. The yields are probably higher since it was very difficult to add the small volume of diazonium salt solution quantitatively to the pyridine. No appreciable quantities of high-boiling residue were obtained when these and subsequent reaction products were distilled under vacuum.

*Determination of Ratios of Isomers formed in the o-Tolylolation of Pyridine.*—The reaction was carried out as described in the general procedure, the amine : pyridine molar ratio being 1 : 260. The reaction mixtures were resolved by g.l.c. on a 4 ft.  $\times$   $\frac{3}{16}$  in. column packed with asphalt

TABLE 3.

Composition (%) mixtures of *o*-tolylpyridines, determined by g.l.c.

- (a) Obtained in presence of air: 2-, 52.7; 3-, 29.7; 4-, 17.6 (mean of 5 experiments).
- (b) Obtained by passing oxygen through the reaction mixture: 2-, 52.0; 3-, 31.4; 4-, 16.6 (mean of 3 experiments).
- (c) Obtained by carrying out the reaction under nitrogen: 2-, 51.5; 3-, 31.0; 4-, 17.5 (mean of 2 experiments).

(10% by weight) on Chromosorb W. The column temperature was 124° and the helium carrier gas flow rate was 50 ml./min. The chromatograms of the reaction mixtures gave three peaks shown to be due to 2-, 3-, and 4-*o*-tolylpyridine (retention times and infrared spectra) and had retention times of 31.5, 36.0, and 39.5 min., respectively. The molar detector responses of these three isomers were the same. Table 3 summarises the results.

*Determination of Overall Yield of the o-Tolylpyridines.*—This was carried out as for the phenylpyridines except that the column temperature was 170° and the retention time was 4.5 min. The average yield accounted for 70–85% of the *o*-toluidine used.

*Determination of Ratios of Isomers formed in the p-Tolylolation of Pyridine.*—The reaction mixtures were resolved as were those of the phenylation of pyridine, but the column temperature was 170° and the helium flow rate 50 ml./min. The peaks due to 2-, 3-, and 4-*p*-tolylpyridine were identified by comparison with the retention times of authentic samples and by the infrared spectra. The three isomers had the same molar detector response. The results are summarised in Table 4.

TABLE 4.

Composition (%) of mixtures of *p*-tolylpyridines, determined by g.l.c.

- (a) Obtained in presence of air: 2-, 58.0; 3-, 26.2; 4-, 15.7 (mean of 3 experiments).
- (b) Obtained by passing oxygen through the reaction mixture: 2-, 54.3; 3-, 29.0; 4-, 16.3 (mean of 3 experiments).
- (c) Obtained by carrying out the reaction under nitrogen: 2-, 55.45; 3-, 29.3; 4-, 15.3 (mean of 2 experiments).

*Determination of Overall Yield of the p-Tolylpyridines.*—Determined as before but using a column temperature of 184°, the results accounted for 70–80% of the *p*-toluidine.

*Determination of the Ratios of Isomers formed in the o-Nitrophenylation of Pyridine.*—The molar ratio of amine : pyridine was 1 : 360 in this case. While 2-*o*-nitrophenylpyridine could be separated readily from the 3- and the 4-isomer by g.l.c. on a variety of columns all attempts to resolve the last two isomers were unsuccessful. The separation and isolation of the combined 3- and 4-*o*-nitrophenylpyridines was carried out by g.l.c. on a 4 ft.  $\times$   $\frac{1}{4}$  in. column packed with asphalt (10% by weight) on acid-washed C-22 firebrick (80–100 mesh), a column temperature of 180° and a helium flow rate of 86 ml./min. being used. Two peaks were observed: the first (retention time 29.5 min.) was due to 2-*o*-nitrophenylpyridine (retention time and infrared spectrum), and the second (retention time 34 min.) was shown to be due to a mixture of 3- and 4-*o*-nitrophenylpyridine in the same way. The compounds representing the second peak were collected quantitatively into a weighed flask cooled in acetone–solid carbon dioxide (for further details see J. G. Saha, Ph.D. Thesis, Saskatoon, 1962). About 15–20 injections were needed to collect a sufficient quantity of material for infrared spectral analysis. Precautions were taken to exclude moisture at all stages. The composition of the mixture was determined by

i.r. spectroscopy.<sup>32</sup> Matched 1.0-mm. cells and carbon tetrachloride solutions were used. 3-*o*-Nitrophenylpyridine exhibited a band at 1195 cm.<sup>-1</sup> in which range the 4-isomer showed no absorption. A calibration curve (straight line) was plotted between the area of this band and the concentration of standard solutions of the 3-isomer. The total weight of the mixture being known it was a simple matter to determine the separate amounts of 3- and 4-*o*-nitrophenylpyridine it contained. The results were: 3-isomer, 87.0; 4-isomer 13.0% (mean of 2 experiments). A synthetic mixture of 3- and 4-*o*-nitrophenylpyridine of this composition was prepared. This was injected on to the same column and under the same conditions as were used for the g.l.c. separation of the mixture of the three isomers, and a calibration curve plotted between the area of peak against weight of sample. A similar curve was obtained for pure 2-isomer. These curves were necessary as the molar detector responses of the three *o*-nitrophenylpyridines were not the same. Reaction mixtures were then analysed under the same conditions. The proportions of 2- and combined 3- and 4-isomers were thus determined to be: 2-isomer, 42.6; 3- and 4-isomer, 57.3% (mean of 3 experiments). From these results and those given above the average percentage composition of the mixture of the three *o*-nitrophenylpyridines was calculated to be: 2-isomer, 42.5; 3-isomer, 50.0; 4-isomer, 7.5%.

The over-all yield of *o*-nitrophenylpyridines, determined as before (column temperature 190°), accounted for 65–75% of the *o*-nitroaniline used.

*Determination of the Ratios of Isomers formed in the p-Nitrophenylation of Pyridine.*—The amine: pyridine molar ratio was 1:360. Again, 2-*p*-nitrophenylpyridine could be readily separated from the 3- and 4-isomers by g.l.c. but the latter two could not be resolved. The separation and isolation of the 3- and 4-*p*-nitrophenylpyridines were carried out by g.l.c. on a 4 ft. ×  $\frac{1}{4}$  in. column packed with a mixture of silicone SE-30 (3% by weight) and asphalt (1% by weight) on Chromosorb W (80 to 100 mesh), using a column temperature of 170° and a helium flow rate of 66 ml./min. The mixture of 3- and 4-*p*-nitrophenylpyridine was collected quantitatively as described for the *ortho*-isomers and analysed by u.v. spectroscopy, the absorbances at 230, 235, 280, and 285 m $\mu$  being used. The solutions obeyed Beer's law. This showed the mixture to contain: 3-isomer, 76.5; 4-isomer, 23.5% (mean of 2 experiments).

The reaction mixture containing the three isomers was now analysed as described for the *o*-nitrophenylpyridines, except that the above column was used. Again, the molar detector responses of the three isomers were different so that a calibration curve was obtained for a synthetic mixture of 3- and 4-*p*-nitrophenylpyridine (in the ratio 77:23). The ratio 2: (3- + 4-) was thereby determined to be: 2-isomer, 44.6; 3- + 4-isomer, 55.3 (mean of three experiments). The average percentage composition of the product of *p*-nitrophenylation was calculated to be: 2-isomer, 44.6; 3-isomer, 42.7; 4-isomer, 12.9%.

The overall yield of *p*-nitrophenylpyridines (column temperature 215°) accounted for 70–80% of the *p*-nitroaniline used; as already explained these estimates are probably low.

*Competitive Experiments.—General procedure.* A solution of the aromatic amine (0.5 g.) in concentrated hydrochloric acid (1.0 ml.) was cooled to 0° and treated with sodium nitrite (0.42 g.) in water (0.75 ml.) at <5°. The diazonium salt solution was added with vigorous stirring during 15 min. to a large excess (amine: solvent, 1:250–390) of a mixture of pyridine and benzene (molar ratio, 4:1 or 6:1) at 40 ± 0.1°. The mixture was stirred for 6 hr. at that temperature, anhydrous sodium carbonate (5 g.) was added, the mixture stirred for a further 15 min. and then kept at room temperature for 24 hr. It was then filtered, the solids washed thoroughly with ether, and the combined filtrates distilled slowly through a fractionating column until only 20–30 ml. of mixture remained. This was transferred quantitatively to a conical flask and used for the quantitative analysis.

*Determination of  $\text{Py}_{\text{Benz}}$ K for phenylation.* The amine: solvent molar ratio was 1:234. When the pyridine: benzene ratio was 1:1 the reaction mixture was heterogeneous; in experiments with molar proportions of 4:1, 5:1, and 6:1 (aromatic amine: solvent ratio still 1:234) the reaction mixtures were homogeneous. The g.l.c. analysis was carried out with 4 ft. ×  $\frac{1}{4}$  in. column packed with Apiezon N (15% by weight) on Chromosorb W (80–100 mesh). The column temperature was 160° and the helium flow rate 120 ml./min. The three isomeric phenylpyridines then had identical retention times (7.4 min.) and were well resolved from biphenyl (4.25 min.). Calibration curves were prepared by using a standard solution of biphenyl and a synthetic mixture of the three phenylpyridines in the ratio found to be present

<sup>33</sup> Augood, Hey, and Williams, *J.*, 1953, 44.



in the isomer-ratio studies. The molar detector responses of biphenyl and of the mixture of phenylpyridines were the same. The results are summarised in Table 5.

TABLE 5.

Determination of  $\frac{\text{Py}}{\text{Benz}}K$  for phenylation.

Expt. No. ....	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47
$n^a$ .....	1:1	1:1	1:1	2:1	2:1	2:1	4:1	4:1	4:1	5:1	5:1	5:1	6:1	6:1	6:1
$\frac{\text{Py}}{\text{Benz}}K$ .....	2.7	2.8	3.0	1.5	1.7	1.6	1.07	1.19	1.17	1.22	1.20	1.14	1.16	1.07	1.10

Mean  $\frac{\text{Py}}{\text{Benz}}K = 1.14$ .

<sup>a</sup>  $n$  = Molar ratio pyridine : benzene.

*Determination of  $\frac{\text{Py}}{\text{Benz}}K$  for o-tolylation.* The amine : solvent molar ratio was 1 : 270—300. The reaction mixtures were analysed by g.l.c. using a 3 ft. column packed as in the previous experiment; the column temperature was 170° and the helium flow rate 120 ml./min. Two peaks were recorded, the first (retention time 2.5 min.) due to 2-methylbiphenyl (retention time and i.r. spectrum) and the second to a mixture of the three o-tolylpyridines. Calibration curves were obtained by using a standard solution of 2-methylbiphenyl and a solution of the three isomeric o-tolylpyridines in the same proportions as had been found in the isomer-ratio studies. The molar detector responses of these compounds were different and the accuracy of the method was again tested on artificial mixtures. Results are recorded in Table 6.

TABLE 6.

Determination of  $\frac{\text{Py}}{\text{Benz}}K$  for o-tolylation.

Expt. No. ....	48	49	50	51	52	53
$n$ .....	4:1	4:4	4:1	6:1	6:1	6:1
$\frac{\text{Py}}{\text{Benz}}K$ .....	1.64	1.67	1.8	1.8	1.70	1.72

Mean  $\frac{\text{Py}}{\text{Benz}}K = 1.72$ .

*Determination of  $\frac{\text{Py}}{\text{Benz}}K$  for p-tolylation.* This was carried out as for the o-tolylation except that the column temperature was 184°. The three p-tolylpyridines had a retention time of 8.0 min. whereas 4-methylbiphenyl had a retention time of 5.4 min. Calibration curves were obtained as before, and the accuracy of the determinations tested on synthetic mixtures. The results are summarised in Table 7.

TABLE 7.

Determination of  $\frac{\text{Py}}{\text{Benz}}K$  for p-tolylation.

Expt. No. ....	54	55	56	57	58	59
$n$ .....	4:1	4:1	4:1	6:1	6:1	6:1
$\frac{\text{Py}}{\text{Benz}}K$ .....	1.40	1.40	1.50	1.45	1.40	1.50

Mean  $\frac{\text{Py}}{\text{Benz}}K = 1.44$ .

*Determination of  $\frac{\text{Py}}{\text{Benz}}K$  for o-nitrophenylation.* This was carried out as for the o-tolylation except that the column temperature was 190°. Two peaks were recorded, the first (retention time 5.25 min.) being due to 2-nitrobiphenyl and the second (retention time 7.1 min.) being due to the mixed o-nitrophenylpyridines. Calibration curves were obtained as before, and the analytical method was shown to be satisfactory by analysis of artificial mixtures. The results are given in Table 8.

TABLE 8.

Determination of  $\frac{\text{Py}}{\text{Benz}}K$  for o-nitrophenylation.

Expt. No. ....	60	61	62	63	64	65
$n$ .....	4:1	4:1	4:1	6:1	6:1	6:1
$\frac{\text{Py}}{\text{Benz}}K$ .....	0.46	0.50	0.47	0.49	0.47	0.45

Mean  $\frac{\text{Py}}{\text{Benz}}K = 0.47$ .

*Determination of  $\frac{\text{Py}}{\text{Benz}}K$  for p-nitrophenylation.* The procedure used was the same as that for o-tolylation, except that the column temperature was 215°. The results obtained are presented in Table 9.

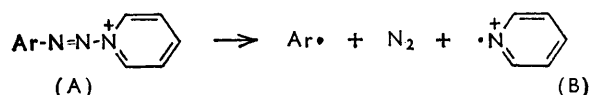
TABLE 9.  
Determination of  ${}_{\text{Benz}}^{\text{Py}}K$  for *p*-nitrophenylation.

Expt. No. ....	66	67	68	69	70	71
<i>n</i> .....	4 : 1	4 : 1	4 : 1	6 : 1	6 : 1	6 : 1
${}_{\text{Benz}}^{\text{Py}}K$ .....	0.78	0.80	0.80	0.77	0.77	0.77

Mean  ${}_{\text{Benz}}^{\text{Py}}K = 0.78$ .

### DISCUSSION

One argument which has been levelled<sup>33</sup> against the suitability of the Gomberg–Hey reaction for quantitative work (particularly in competitive reactions) is the fact that with the usual aromatic solvents the reaction is a heterogeneous one. In the present instance, the mixtures were homogeneous. Selective solvation was not important within the solvent-ratio range used. Pyridine may cause the isomerisation of the diazonium salt to give either the diazo-hydroxide in the presence of water<sup>8</sup> ( $pK_a$  of pyridine is 5.21), or the complex (A)<sup>8</sup> in which case the decomposition could proceed thus:



(B) could abstract a hydrogen atom from the  $\sigma$ -complex to give the pyridinium cation.

No high-boiling residues could be detected in the present work. It is believed that the errors in the quantitative estimations are small, since the procedure involves as few steps as possible. The values obtained were found to be reproducible within  $\pm 2\%$  (in most cases better).

Oxygen is seen to have no appreciable effect upon the proportions of isomers formed in the phenylation and *o*-tolylation of pyridine, and any small differences observed are within the experimental error and are entirely random. The effect of oxygen upon the yields of arylpyridines was examined briefly, and only in the case of phenylation, where a slight diminution in overall yield observed. Further work is necessary to confirm this observation. In the *p*-tolylation reactions, the difference between the ratios obtained in the presence of air and in the presence of oxygen are somewhat larger. Any significance that might be attributed to this observation seems to be vitiated by the fact that when the measurements were made on reactions carried out under nitrogen the isomer ratios were almost the same as those obtained when oxygen was bubbled through the reaction mixtures. The absence of an "oxygen effect" on the isomer ratios might be explained either by assuming that under the present reaction conditions there is no selective removal of the isomeric aryldihydropyridyl radicals formed, or that a "cage-process" is involved in which an aryl radical and a hydroxyl radical or pyridinium radical cation (B) are generated simultaneously, the former adding to a molecule of the surrounding pyridine solvent to form the  $\sigma$ -complex and either of the latter abstracting a hydrogen atom from it before it has had time to diffuse out of the solvent cage. The observed isomer ratios can, therefore, be taken as a measure of the relative reactivities of the nuclear positions in pyridine towards the aryl radical under study. The same point has been stressed recently by Morrison and his co-workers.<sup>16</sup> Eliel *et al.*<sup>17</sup> have suggested a "cage-process" (or diffusion-controlled reaction) for the decomposition of *N*-nitrosoacetanilide in benzene. In view of the similarity between the decomposition of acylarylnitrosamines and the Gomberg–Hey reaction it appears likely that the homolytic substitution stages in both of these reactions proceed by a similar mechanism. Further support for the concept that there is no selective removal of the isomeric  $\sigma$ -complexes in such reactions comes from the observations of the so-called nitro-group effect in the phenylation of fluorobenzene with

<sup>33</sup> Williams, "Homolytic Aromatic Substitution," Pergamon Press, London, 1960.

benzoyl peroxide.<sup>34</sup> Finally, no appreciable isotope effect has been observed in the decomposition of various benzenediazonium salts in deuterobenzene under the conditions of the Gomberg–Hey reaction.<sup>35</sup>

The relative rates of arylation with *o*-tolyl and *o*-nitrophenyl radicals are compared in Table 10 with those of phenylation and arylation with the corresponding *para*-substituted radicals.

TABLE 10.

Relative rates of arylation of pyridine at 40° and of nitrobenzene at 80°.

Radical	Ph•	<i>o</i> -Me·C <sub>6</sub> H <sub>4</sub> •	<i>p</i> -Me·C <sub>6</sub> H <sub>4</sub> •	<i>o</i> -NO <sub>2</sub> ·C <sub>6</sub> H <sub>4</sub> •	<i>p</i> -NO <sub>2</sub> ·C <sub>6</sub> H <sub>4</sub> •
<sup>Py</sup> K Benz	1.14	1.72	1.44	0.47	0.78
<sup>PhNO<sub>2</sub></sup> K* Benz	2.94		3.4	0.26	0.94

\* Radical generated from diaryl peroxides; see ref. 36.

The values are in good agreement with the concept of polarised radicals<sup>33</sup> and with the known behaviour of pyridine towards electrophilic and nucleophilic reagents. The spread of values obtained for <sup>Py</sup>K is smaller than that for <sup>PhNO<sub>2</sub></sup>K. On the other hand, the isomer ratios (see below) are much more sensitive to the polarity of the radical in the case of pyridine than in that of nitrobenzene.

The averaged proportions of isomeric arylpyridines formed in the phenylations and tolylations in the presence of air, oxygen, or nitrogen are summarised in Table 11, together with the data for the nitrophenylation reactions (in the presence of air).

TABLE 11.

Averaged ratios of *r*-arylpyridines formed in the arylation of pyridine (%).

Radical	2-	3-	4-	Radical	2-	3-	4-
Ph•	52.4	29.6	18.0	<i>o</i> -NO <sub>2</sub> ·C <sub>6</sub> H <sub>4</sub> •	42.6	50.0	7.5
<i>o</i> -Me·C <sub>6</sub> H <sub>4</sub> •	52.1	30.7	17.2	<i>p</i> -NO <sub>2</sub> ·C <sub>6</sub> H <sub>4</sub> •	44.6	42.7	12.9
<i>p</i> -Me·C <sub>6</sub> H <sub>4</sub> •	56.0	28.2	15.8				

As can be predicted on the basis of the “electrophilic character” of the nitrophenyl radicals and the “nucleophilic character” of the tolyl radicals (compared with phenyl itself), the proportion of  $\alpha$ -isomer formed in the reaction with the *p*-tolyl radical is higher than that formed with the phenyl radical, and the proportion of  $\beta$ -isomer formed in the *o*-nitrophenylation of pyridine is appreciably higher than that in phenylation, to the extent that it becomes the main isomer (thus confirming qualitative observations<sup>8</sup>), contrary to the general assumption that the  $\alpha$ -isomer is always formed predominantly in such reactions. On the other hand, the proportion of  $\alpha$ -isomer formed with *o*-tolyl radicals should have been higher than that with *p*-tolyl radicals, steric effects being assumed to be absent: unexpectedly, it is very slightly lower than that formed with phenyl radicals and appreciably lower (outside the limits of experimental error) than that formed with *p*-tolyl radicals.

TABLE 12.

Partial rate factors for the arylation of pyridine at 40° in the presence of air (oxygen).

Radical	$f_{\alpha}$	$f_{\beta}$	$f_{\gamma}$	Radical	$f_{\alpha}$	$f_{\beta}$	$f_{\gamma}$
Ph•	1.83(1.78)	1.00(1.02)	1.18(1.23)	<i>o</i> -NO <sub>2</sub> ·C <sub>6</sub> H <sub>4</sub> •	0.60	0.71	0.21
<i>o</i> -Me·C <sub>6</sub> H <sub>4</sub> •	2.72(2.68)	1.53(1.62)	1.82(1.71)	<i>p</i> -NO <sub>2</sub> ·C <sub>6</sub> H <sub>4</sub> •	1.03	1.00	0.60
<i>p</i> -Me·C <sub>6</sub> H <sub>4</sub> •	2.51(2.35)	1.13(1.25)	1.36(1.41)				

The partial rate factors for the arylation of pyridine at 40° in the presence of air are assembled in Table 12. The value in parentheses refer to the partial rate factors calculated by using the isomer ratios obtained when the reactions were carried out while passing

<sup>34</sup> Hey, Perkins, and Williams, *Chem. and Ind.*, 1963, 83.

<sup>35</sup> Eliel and Saha, private communication.

<sup>36</sup> Williams, *Chem. and Ind.*, 1961, 1285.

oxygen through the mixtures. In all cases the arithmetic means of the ratios of isomers and of the total rate factors were used.

The range in partial rate factors is small but significant as the differences observed are outside the error of experiment. The partial rate factors for the phenylation of pyridine (benzoyl peroxide being used at 80°) had previously been reported<sup>23</sup> to be:  $f_\alpha = 1.8$ ,  $f_\beta = 0.87$ ,  $f_\gamma = 0.87$ , which differ from the values obtained in the present work. This may be a reflection of the influence of the lower temperature and/or of the different arylating agent used. It has already been mentioned that the use of benzoyl peroxide may give rise to some pyridine 1-oxide.<sup>13</sup> That the pyridine ring is more sensitive to the polarity of the attacking radical is seen clearly from a comparison of the partial rate factors for the *o*-nitrophenylation of nitrobenzene ( $f_o = 0.43$ ,  $f_m = 0.14$ ,  $f_p = 0.42$ )<sup>3</sup> and of pyridine, for example.

The ratios of isomers obtained in these arylations should reflect the polar character of the substituted phenyl radicals in a predictable manner. No calculations have, however, been published that could give an indication of the relative susceptibilities of the nuclear positions in an aromatic compound to attack by polar free radicals. It might be possible to make some tentative predictions based on a superposition of the known behaviour of pyridine towards phenyl radicals, nucleophilic and electrophilic reagents and by making the assumptions (a) that the transition state for such substitutions is similar in geometry to that postulated by Weingarten,<sup>9</sup> namely that in the transition state the attacking radical is almost perpendicular to the plane of the substrate ring and sufficiently far from it that  $\pi$ -electron-densities in the molecule being attacked have not been appreciably "perturbed," and (b) that steric effects due to *ortho*-substituents are, at most, minor in the arylation of pyridine. If (a) holds it is likely that the susceptibility of the various nuclear positions in pyridine towards attack by polar reagents will follow the order of the ground state  $\pi$ -electron-densities.<sup>37,38</sup> Thus, the ease of attack of the various positions in pyridine by nucleophilic reagents should follow the order  $\alpha > \gamma \gg \beta$ , and that by electrophilic reagents the order  $\beta > \gamma > \alpha$ .

On this basis one can make some tentative conclusions concerning the relative magnitudes of the ratios of the partial rate factors. For instance,  $f_\alpha/f_\beta$  should follow the order *o*-tolyl > *p*-tolyl > phenyl, provided assumption (b) holds. Similarly, the ratio  $f_\alpha/f_\gamma$  should be in the order *o*-tolyl > *p*-tolyl > phenyl. The observed  $f_\alpha/f_\beta$  ratios for the tolylations and phenylation follow the order *p*-tolyl > phenyl > *o*-tolyl, while the observed  $f_\alpha/f_\gamma$  ratios are also in that order, contrary to the prediction made above (see Table 13). These results indicate that less  $\alpha$ -isomer is formed than expected in the

TABLE 13.

Ratios of partial rate factors for the arylation of pyridine at 40° (in the presence of air).

Radical	$f_\alpha/f_\beta$	$f_\alpha/f_\gamma$	$f_\beta/f_\gamma$	Radical	$f_\alpha/f_\beta$	$f_\alpha/f_\gamma$	$f_\beta/f_\gamma$
Ph· .....	1.83	1.57	0.86	<i>o</i> -NO <sub>2</sub> ·C <sub>6</sub> H <sub>4</sub> · .....	0.85	2.88	3.39
<i>o</i> -Me·C <sub>6</sub> H <sub>4</sub> · .....	1.77	1.50	0.85	<i>p</i> -NO <sub>2</sub> ·C <sub>6</sub> H <sub>4</sub> · .....	1.05	1.71	1.66
<i>p</i> -Me·C <sub>6</sub> H <sub>4</sub> · .....	2.22	1.85	0.83				

*o*-tolylation of pyridine. A similar result is obtained if the ratios of partial rate factors are based on the isomer ratios obtained when oxygen was passed through the reaction mixtures.

Again, one would expect the  $\beta$ -position of pyridine to be most and the  $\alpha$ -least affected by a change in the electrophilic character of the attacking reagent. Thus, as the electrophilic character of the latter increases (*o*-nitrophenyl > *p*-nitrophenyl > phenyl) one might expect  $f_\beta$  to increase and  $f_\gamma$  to decrease relatively less than  $f_\alpha$ . This leads to the prediction that  $f_\alpha/f_\beta$  should be in the order phenyl > *p*-nitrophenyl > *o*-nitrophenyl, which

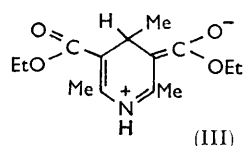
<sup>37</sup> Brown and Harcourt, *J.*, 1959, 3451.

<sup>38</sup> Hammond, *J. Amer. Chem. Soc.*, 1955, 77, 334.



is the order observed experimentally. The predicted order of  $f_\beta/f_\gamma$  on this basis is *o*-nitrophenyl > *p*-nitrophenyl > phenyl, and this also is found. Abnormality in the behaviour of *o*-nitrophenyl radicals is, however, shown by the  $f_\alpha/f_\gamma$  ratio. The predicted order for this ratio on the above assumptions is phenyl > *p*-nitrophenyl > *o*-nitrophenyl; that observed is *o*-nitrophenyl > *p*-nitrophenyl > phenyl. Whereas the observed values of  $f_\alpha/f_\gamma$  for *p*-nitrophenyl and phenyl radicals are in the reverse order to those predicted the difference between them is small compared with the difference between the values for *o*- and *p*-nitrophenylation. It appears, therefore, that more  $\alpha$ -isomer is formed with the *o*-nitrophenyl radical than predicted.

If these observations are real, and not merely the fortuitous results of the assumptions made above, they might be rationalised by postulating a new type of “*ortho*-effect,”



namely: (i) a *repulsion* between the *ortho*-methyl group of the *o*-tolyl radical and the lone-pair of electrons on the pyridine nitrogen atom in the transition state leading to  $\alpha$ -substitution, and (ii) an *attraction* between the *o*-nitro-group in the attacking radical and the pyridine nitrogen lone-pair in the corresponding transition state.

A similar non-bonded repulsion has been postulated<sup>39</sup> in the electronically excited state (III) of diethyl 1,4-dihydro-2,4,6-trimethylpyridine-3,5-dicarboxylate.

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<sup>39</sup> Hofmann, Kosower, and Wallenfels, *J. Amer. Chem. Soc.*, 1961, **83**, 3314.