ARYLPYRIDINES

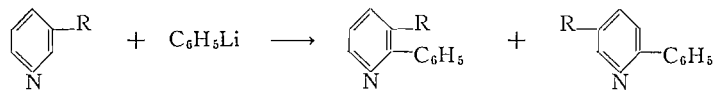
PART II. REACTION OF PHENYLLITHIUM WITH 3-METHOXY- AND 3-AMINO-PYRIDINE[1,2]

R. A. Abramovitch and A. D. Notation

ABSTRACT

Phenyllithium has been shown to react with 3-methoxy- and 3-amino-pyridine to give exclusively 3-methoxy-2-phenylpyridine and 3-amino-2-phenylpyridine respectively. The orientation of the products has been established unambiguously. None of the 2,5-isomer was detected in either case. An explanation for this unique orientation is suggested.

In Part I of this series (1) the orientation of the entering phenyl substituent in the addition of phenyllithium to 3-picoline and to nicotine was studied. In the first case the main product was 3-methyl-2-phenylpyridine (II; R = CH_3) together with a small amount of 5-methyl-2-phenylpyridine (III; R = CH_3), the ratio of the isomers being 19:1. On the other hand phenylation of nicotine gave 2-phenyl- (II; R = -α-$C_4H_7NCH_3$) and 6-phenyl-nicotine (III; R = -α-$C_4H_7NCH_3$) in a 1:1 ratio. Evidence that the 3-substituent exerts an appreciable steric effect in the end product of the addition was



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also presented. The results were interpreted to mean that addition of phenyllithium to 3-substituted pyridines occurs preferentially at the 2-position but that the 3-substituent, if sufficiently bulky, could exert a steric effect resulting in appreciable addition at the 6-position also.

The present paper gives an account of the extension of this study to 3-amino- and 3-methoxy-pyridines both of which are readily available and the products from which could serve as valuable intermediates in synthetic work. Molecular models indicate that the steric effect of a methoxyl group would be expected to be less than that of a methyl group whereas that of a primary amino group, particularly as its lithium salt, should be comparable with that of a methyl group. 3-Methoxypyridine was prepared by methylation of 3-hydroxypyridine according to Prins's procedure (2).

3-Aminopyridine (I; R = NH_2) was treated with a 3-molar excess of phenyllithium to give a 24.5% yield of product. That probably only a single isomer was present was indicated by vapor phase and by column chromatography, and that this isomer was 3-amino-2-phenylpyridine (II; R = NH_2) was shown by comparison of the base and of its picrate with authentic specimens prepared unambiguously from 3-methyl-2-phenylpyridine (3). No evidence for the presence of any 5-amino-2-phenylpyridine in the mixture could be obtained.

In a similar manner, 3-methoxypyridine reacted with phenyllithium to give a 21.2% yield of product $C_{12}H_{11}ON$. Once again this was shown chromatographically to consist

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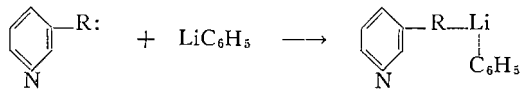
of a single isomer which proved to be 3-methoxy-2-phenylpyridine. This could be established quite readily by demethylation to 3-hydroxy-2-phenylpyridine, an authentic specimen of which was obtained from the above 3-amino-2-phenylpyridine. The physical properties of the phenol corresponded also to those reported for 3-hydroxy-2-phenylpyridine (II; R = OH) by Leditschke (4). The infrared spectrum of 3-methoxy-2-phenylpyridine exhibited a band at 1584 cm^{-1} which has been shown to be characteristic of such 2,3-disubstituted pyridine derivatives (5). Once again no 5-hydroxy-2-phenylpyridine was detected in the crude reaction product.

It would seem, therefore, that in the present instance the entering phenyl group is directed *exclusively* to the 2-position. A possible explanation of this observation is that in both the examples studied here the 3-substituent has a pair of electrons which can co-ordinate with the lithium atom to form a complex such as IV in which the phenyl group would be suitably oriented for attack at the 2-position. This, together with the already established tendency for preferential addition to the 2-position (1), would account for the fact that no 6-substitution was observed. Stereospecificity in the addi-



IV

tion of phenyllithium to α-hydroxyketones has been similarly attributed to the formation of a lithium complex as an intermediate (6).

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were measured using a Perkin–Elmer Model 21 instrument and the vapor phase chromatographic work was carried out using a Beckman GC-2 unit with helium as the carrier gas.

Reaction of Phenyllithium with 3-Aminopyridine

Lithium (1.65 g) was finely cut and suspended in anhydrous ether (50 ml) under dry nitrogen. Bromobenzene (11.4 ml; 17 g) in anhydrous ether (20 ml) was added dropwise at such a rate as to maintain gentle reflux. When the formation of phenyllithium was complete 3-aminopyridine (4 g) in anhydrous ether (80 ml) was added over a period of 20 minutes during which time a brilliant yellow suspension was formed. The ether was distilled off and simultaneously replaced by dry toluene (100 ml) and the temperature was raised to the boiling point. The mixture was boiled under reflux with stirring for $7\frac{1}{2}$ hours during which time the color turned a dark brown. Water was carefully added to the cold suspension, the toluene layer separated, and the aqueous layer extracted repeatedly with ether. The combined ether and toluene layers were extracted with dilute hydrochloric acid, the acid extract made strongly basic with sodium hydroxide, and the product extracted with ether. The ether layer was dried (Na_2SO_4), evaporated, and the residue distilled under vacuum to give crude 3-amino-2-phenylpyridine (1.5 g). This was redistilled and obtained as a pale yellow oil, b.p. 119–121°/0.35 mm, which solidified on cooling and was recrystallized from benzene – light petroleum (b.p. 40–60°) giving colorless crystals, m.p. 62–64°. Calc. for $C_{11}H_{10}N_2$: C, 77.62; H, 5.92. Found: C, 77.90; H, 5.78. Infrared spectrum (Nujol mull) (main peaks only): 3350 (m) (br), 3220 (m) (br), 1620 (s) (br), 1585 (s), 798 (s), 743 (s), 730 (w), 695 cm^{-1} (w).

The monopicrate, on recrystallization from ethanol, had a melting point of 204–206°. Calc. for $C_{11}H_{10}N_2$, $C_6H_3O_7N_3$: C, 51.13; H, 3.28. Found: C, 51.18; H, 3.17.

A sample of crude reaction product (0.1193 g) was chromatographed on a narrow column of alumina (5 g). Elution was carried out using the following sequence of solvents: light petroleum (b.p. 40–60°), benzene – light petroleum, benzene, benzene–ether, ether, ether–methanol, and finally methanol. Only a single colorless band, exhibiting blue fluorescence under ultraviolet light was eluted, and this with benzene–ether. Different portions of the benzene–ether eluate were converted to the picrate. In each case, only 3-amino-2-phenylpyridine picrate, m.p. 204–206°, was obtained. Also, the individual fractions had identical infrared spectra. The total recovery from the column was 0.1018 g. The mixed melting point of the picrate with that of an authentic sample (3) was undepressed. Also, the infrared spectrum of the free base was identical with that of the authentic sample. Only one peak was observed on vapor phase chromatography of the crude free base under a variety of conditions.

Reaction of Phenyllithium with 3-Methoxypyridine

Phenyllithium was prepared from lithium (0.5 g) and bromobenzene (5.7 g) in anhydrous ether. 3-Methoxypyridine (4 g) in anhydrous ether (30 ml) was added dropwise over a period of 20 minutes, after which the ether was distilled off and simultaneously replaced by dry toluene (40 ml). The reaction mixture was stirred and boiled under reflux under an atmosphere of nitrogen for 7 hours, water was carefully added to the cooled suspension, and the toluene layer separated. The aqueous layer was extracted with ether, the combined ether and toluene extracts washed with dilute hydrochloric acid, and the acid solution basified and extracted with ether. The dried (Na_2SO_4) ether extract was evaporated and the residue distilled under vacuum, the fraction (1.4 g), b.p. 120–160°/0.34 mm, being collected. Redistillation gave pure 3-methoxy-2-phenylpyridine, b.p. 110–112°/0.34 mm. Calc. for $C_{12}H_{11}ON$: C, 77.81; H, 5.99. Found: C, 78.13; H, 6.43. Infrared spectrum (liquid film) (main peaks only): 1575 (s), 1265 (s) (br), 1195 (s), 1125 (s), 1015 (s), 795 (s), 735 (s), 692 cm^{-1} (s).

The picrate was recrystallized from ethanol and had a melting point of 153.5–155°. Calc. for $C_{12}H_{11}ON$, $C_6H_3O_7N_3$: C, 52.18; H, 3.41. Found: C, 52.53; H, 3.86.

The crude base was shown to consist of a single compound by column and vapor phase chromatography as described for 3-amino-2-phenylpyridine.

3-Hydroxy-2-phenylpyridine

(i) From 3-Methoxy-2-phenylpyridine

3-Methoxy-2-phenylpyridine (0.2 g) was boiled under reflux for 4 hours with 47% hydrobromic acid (3 ml). The excess hydrobromic acid was then evaporated off and the residue neutralized with 10% sodium carbonate solution and ether extracted. The dried (Na_2SO_4) ether extract was evaporated and the residue of 3-hydroxy-2-phenylpyridine recrystallized from ethanol to give colorless crystals, m.p. 206–207.5°. Leditschke (4) reported a melting point of 205° for this compound. The infrared spectrum of this product was identical with that of an authentic specimen prepared as described under (ii) below. Also, its melting point was undepressed on admixture with the authentic specimen.

(ii) From 3-Amino-2-phenylpyridine

3-Amino-2-phenylpyridine (0.4 g) was dissolved in a mixture of concentrated sulphuric acid (0.8 ml) and water (2 ml). The solution was cooled to 0–5° and diazotized with sodium nitrite (0.3 g) in water (1 ml) and after $\frac{1}{2}$ hour at 0–5° the excess nitrous acid

was decomposed with urea. The solution was then boiled under reflux for 1 hour after which time it gave a negative alkaline β-naphthol test. The reaction mixture was treated with solid sodium carbonate and ether extracted repeatedly. The combined ether extracts were dried (K_2CO_3) and evaporated giving crude 3-hydroxy-2-phenylpyridine (0.35 g) contaminated with some orange impurity. Recrystallization from ethanol gave the pure phenol, m.p. 206–207.5°. Infrared spectrum (Nujol mull) (main peaks only): 1573 (m), 1280 (s) (br), 1182 (s), 1115 (m), 802 (m), 735 (s), 693 cm^{-1} (m).

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