# Transformations in the Pyridine Series. An Improved Preparation of 3-Methyl-4-phenylpyridine

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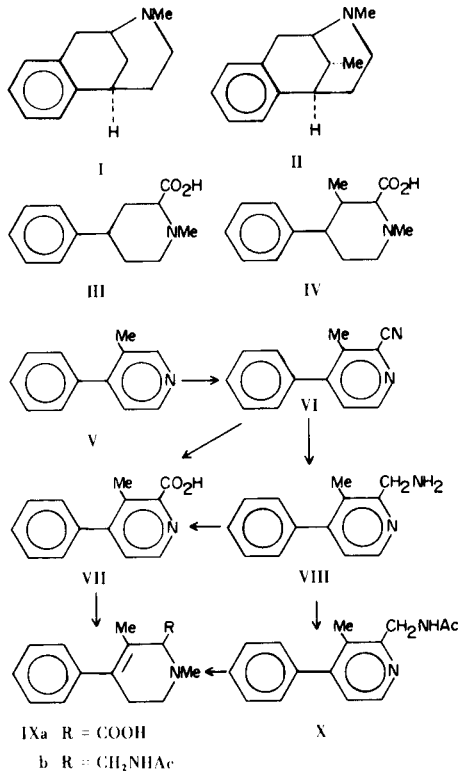
An improved, large-scale preparation of 3-methyl-4-phenylpyridine (V) is described. This compound was converted to 3-methyl-4-phenylpicolinic acid (VII) which could not be reduced to the desired piperidine congener (IV).

An alternative sequence in the synthesis of 2-methyl-6,7-benzomorphan (I) involves polyphosphoric acid cyclization (3) of 2-carboxy-1-methyl-4-phenylpiperidine (III). We attempted to utilize this route to prepare the 9-methyl derivative (II) of I (4) which would require 2-carboxy-1,3-dimethyl-4-phenylpiperidine (IV). Although we were unable to obtain IV, some reactions toward it and an improved, large-scale preparation of 3-methyl-4-phenylpyridine (V) (5) may be of interest.




Compound V was prepared by aromatization of a mixture (6) of 1,3-dimethyl-4-phenyl-1,2,5,6-tetrahydropyridine and the corresponding 1,2,3,6-tetrahydro isomer using palladium on alumina (7) and converted in a standard way (4,8) to 2-cyano-3-methyl-4-phenylpyridine (VI). Hydrogenation of VI (which could not be quaternized with methyl iodide or dimethyl sulfate) with palladium on charcoal gave 2-aminomethyl-3-methyl-4-phenylpyridine (VIII), acetylation of which (acetic anhydride) yielded X. Hydrolysis of VI with potassium hydroxide in ethylene glycol or hydrochloric-acetic acid gave 3-methyl-4-phenylpicolinic acid (VII) in 96 and 64% yields, respectively. This acid also resulted from oxidation of VIII. Reduction of the methiodides of VII and X with sodium borohydride gave (based on spectral data) tetrahydro derivatives IXa and IXb, respectively, which could not be further reduced to IV and the piperidine derivative corresponding to IXb.

## EXPERIMENTAL

Melting points (Hershberg) are corrected. Ir, nmr, uv and mass spectra were recorded on a Perkin-Elmer 257, a Varian Model A-60-A, a Beckmann DB-G and a Hitachi RMU-6E (70 eV), respectively, and are in accord with the structures shown. Some of these data and the carbon-hydrogen-nitrogen analyses are from the Section on Instrumentation and Analytical Services of this laboratory. Magnesium sulfate was the drying agent used.

3-Methyl-4-phenylpyridine (V).

A mixture of 110 g. of diastereomeric 1,3-dimethyl-4-phenyl-4-piperidinols (9,10) was dehydrated to the corresponding $\Delta^3$- and $\Delta^4$-piperidines according to Casy, *et al.* (6). The latter mixture (86 g.), 200 g. of nitrobenzene and 4 g. of palladium on alumina (7) were kept at 130-140° for 3.5 hours, cooled, treated with 250 ml. of 12% hydrochloric acid and extracted with 800 ml. of toluene in four portions. The toluene extract was shaken with dilute hydrochloric acid. The combined acid extracts were filtered through Norit and made alkaline with sodium hydroxide. Extraction with

benzene and drying and evaporation of solvent left a dark-colored liquid which gave 50.5 g. (59%) of V, b.p. 96-98° (0.2 mm.). Its nmr spectrum and picrate were in agreement with those reported earlier (5).

2-Cyano-3-methyl-4-phenylpyridine (VI).

To V (17 g.) in 60 ml. of acetic acid was added 12 ml. of 30% hydrogen peroxide. The mixture was kept at 75-85° for 3 hours and treated with an additional 9 ml. of the peroxide; heating was continued for 12 hours. Most of the acetic acid was evaporated at reduced pressure, and water (100 ml.) was added. The mixture was made basic with 10% sodium hydroxide. Extraction with chloroform and drying and evaporation of the chloroform gave 17 g. of the crude *N*-oxide, m.p. 130° (after a recrystallization from acetone) whose nmr spectrum was in agreement with the assigned structure.

This *N*-oxide (51 g.) and 40 g. of dimethyl sulfate were heated at 90-100° (bath temperature) for 2 hours. The resulting methosulfate was dissolved in 200 ml. of 95% methanol and added to a stirred solution of 39 g. of sodium cyanide in 300 ml. of water at 15-20°. The mixture was stirred for 4 hours at room temperature and extracted with chloroform (3 x 200 ml.). The dried extract, on evaporation, gave 42 g. of VI, m.p. 113-114°, after a recrystallization from acetone-ether.

*Anal.* Calcd. for $C_{13}H_{10}N_2$: C, 80.38; H, 5.19; N, 14.42. Found: C, 80.59; H, 5.23; N, 14.46.

2-Aminomethyl-3-methyl-4-phenylpyridine (VIII) Hydrochloride.

Nitrile VI (500 mg.), 50 mg. of 10% palladium on charcoal and 25 ml. of acetic acid were shaken at room temperature and pressure to cessation of absorption of hydrogen. After removal of catalyst (filtration) and acetic acid (distillation at reduced pressure), the residue was dissolved in water and made basic with 12 *M* ammonium hydroxide. Extraction with ether and drying and evaporation of the extracts gave an oil which was converted to 580 mg. of hydrochloride (550 mg., 79.1%) m.p. 211-215° after a recrystallization from ethanol-ether; λ max (ethanol): 208 (ε, 26,000), 239 (ε, 1,100), 268 (ε, 5,100) nm; mass spectrum: 198 ($M^+$), 197 (base), 181, 180, 170, 169, 168.

Compound VIII (free base) was converted (77% yield) to the *N*-acetyl derivative (X) with acetic anhydride at room temperature; m.p. 106-107° (from isopropyl ether); ν max (nujol): 3300, 1645, 1630 $cm^{-1}$.

*Anal.* Calcd. for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 75.16; H, 6.92; N, 11.72.

3-Methyl-4-phenylpicolinic acid (VII).

A mixture of VI (1.1 g.), 1 g. of potassium hydroxide, 5.5 ml. of water and 22 ml. of ethylene glycol was kept at 120-130° (bath temperature) for 20 hours, poured into ice-water (20 ml.), treated with acetic acid to *p*H 5-6, and extracted with chloroform. The extracts were dried and evaporated to give a colorless solid which was recrystallized from ethyl acetate to give prisms (1.2 g., 96%), m.p. 165-166°; ir (chloroform): ν 3200, 1765, 1350, 1420 $cm^{-1}$.

*Anal.* Calcd. for $C_{13}H_{11}NO_2$: C, 73.23; H, 5.20; N, 6.57. Found: C, 72.97; H, 5.00; H, 6.50.

Hydrolysis of VI with 12 *M* HCl-acetic acid gave a 64% yield of VII.

Oxidation of VIII to VII.

A mixture of 350 mg. of VIII (free base), 3.8 g. of manganese dioxide-charcoal (11) and 40 ml. of carbon tetrachloride was stirred at room temperature for 4 days, filtered and evaporated to dryness to give 220 mg. of crude aldehyde; ir (chloroform): ν 1710 $cm^{-1}$. To a mixture of this aldehyde, 560 mg. of silver nitrate and 36 ml. of 90% ethanol, was added during 20 minutes at room temperature (stirring), 15 ml. of 0.5 *N* sodium hydroxide. Stirring was continued for 20 hours. Insoluble material was filtered and washed with water (50 ml.). The filtrate was acidified with acetic acid and extracted with chloroform. Drying and evaporation of the extract left a residue which was dissolved in ether. The ether was shaken with aqueous sodium hydroxide. Acidification of the aqueous extract (to *p*H 5-6) with acetic acid and extraction with chloroform gave after drying and evaporation of the chloroform, a residue which crystallized from chloroform-ether; yield 40 mg. (12.7%), m.p. 165-166°.

2-Carboxy-1,3-dimethyl-4-phenyl-1,2,5,6-tetrahydropyridine (IXa).

Methyl iodide (1 g.), 950 mg. of VII and 6 ml. of dimethylformamide were kept at 80° for 2.5 hours and evaporated to dryness *in vacuo*. The residual methiodide, 30 ml. of methanol and 18 ml. of *N* potassium hydroxide were treated with 1.2 g. of sodium borohydride (ice cooling) and the mixture was stirred at 25° for 3 hours. Addition of 100 ml. of water and extraction with ether gave (from the ether layer) 49 mg. (5.9%) of 1,3-dimethyl-3-phenyl-1,2,5,6-tetrahydropyridine (6). The water layer was treated with acetone, acidified with acetic acid and evaporated to dryness *in vacuo*. The residue was dissolved in 50 ml. of ethanol. Addition of 200 ml. of methylene chloride gave inorganic material (on overnight standing) which was filtered. The filtrate was evaporated *in vacuo*. This process was repeated twice with chloroform to give 900 mg. of gummy product (IXa) which was homogeneous (thin-layer chromatography); ir (chloroform): ν 3350 (w), 2800-2400 (s), 1710 (w), 1630 (s), 1400 (s) $cm^{-1}$; mass spectrum: 231·1259 (calcd. for $C_{14}H_{17}NO_2$, 231·1258) 186 (base), 172.

Similar reduction of X gave an 89% yield of pale-yellow, oily material which appears to be IXb; ir (neat): ν 3300, 3070, 2790, 1655, 1440, 1300 $cm^{-1}$; nmr (carbon tetrachloride): δ 1.57 (s, broad, 3H, C-3 $CH_3$), 1.89 (s, 3H, $COCH_3$), 2.1-2.4 (m, 2H, C-5 H), 2.44 (s, 3H, $NCH_3$), 2.5 and 3.6 (m, 5H, NCH), 6.7 and 7.4 (m, 5H, aromatic).

Hydrogenation of the methiodide of either VII or X (platinum oxide, methanol) did not proceed at all. Furthermore, attempts to reduce IXa or IXb to the corresponding piperidines were unsuccessful.

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