

TRANSFORMATIONS IN THE PYRIDINE SERIES. A SIMPLE PREPARATION OF  
3-METHYL-4-PHENYLPYRIDINE AND CORRESPONDING 2-CARBOXAMIDES

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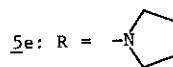
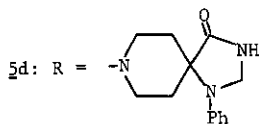
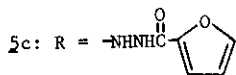
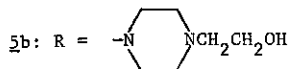
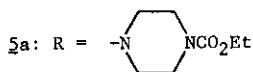
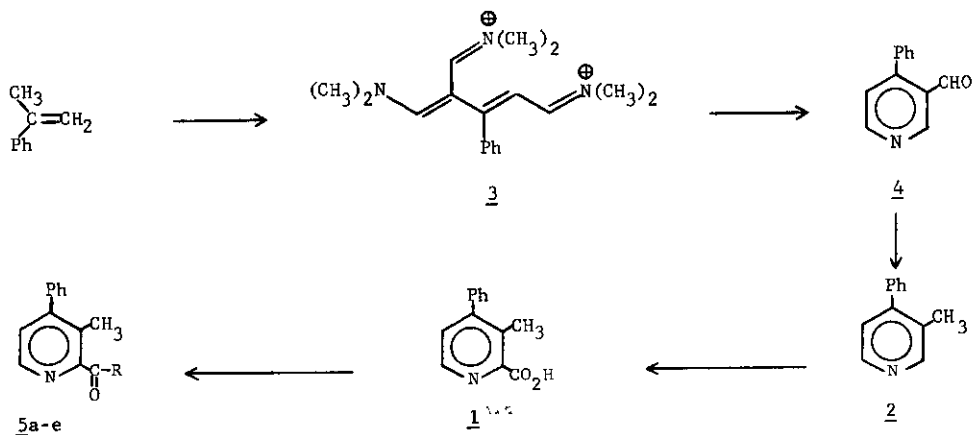
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Abstract - A simple 3-step synthesis of 3-methyl-4-phenylpyridine (2), a key intermediate in the synthesis of several diverse types of potential pharmaceutical agents is reported. Conversion of this pyridine derivative, which is easily prepared on a large scale, to a number of the corresponding 2-carboxamides is described. Amide 5a of this series was active as a basic, nonsteroidal anti-inflammatory agent in the rat adjuvant arthritis test.

For work in progress in our laboratory we required relatively large quantities of a number of amides of 3-methyl-4-phenylpyridine-2-carboxylic acid (1). The most attractive starting material for this work seemed to be 3-methyl-4-phenylpyridine (2), a key intermediate previously utilized in our laboratory for a projected synthesis of analgesic 6,7-benzomorphans.<sup>2</sup> In this work, synthesis of 2 was accomplished in 3 steps from 1,3-dimethyl-4-piperidone (prepared in 4 steps from acyclic materials<sup>3</sup>) via a difficult aromatization involving expulsion of the N-methyl group. Other syntheses of 2 have been reported which either involve lengthy sequences or relatively unavailable starting materials.<sup>4,5,6</sup> In addition to these, Russian workers reported<sup>7</sup> a preparation of 2 which, in our hands, proved to be rather cumbersome and did not proceed well.

For our synthesis, we utilized the report of Jutz<sup>8</sup> who showed that  $\alpha$ -methylstyrene, oxalyl chloride and dimethylformamide produced iminium salt 3 (quantitative yield) which on treatment with aqueous ammonium chloride afforded 4-phenylpyridine-3-carboxaldehyde (4). Although

these workers presented no yield data on the conversion of 3 into 4 we found that the transformation is quite efficient (96% isolated yield). Simple Huang-Minlon reduction of 4 proceeded readily in 89% yield to give 2 in a state of high purity which was identical with an authentic sample. Conversion of 2 to carboxylic acid 1 was smoothly carried as previously described.<sup>2</sup>



It is of interest to note that the sequence starting with  $\alpha$ -methylstyrene and proceeding through 2 represents a possible route to 4-aryl-3-methylpyridines containing various base-stable substituents on the phenyl ring. Given the known difficulty of obtaining 3,4-disubstituted pyridines in general, the synthetic possibilities of this route seem worthy of further exploration. Of course, to be useful such a general synthesis requires that the necessary  $\alpha$ -methylstyrenes be reasonably accessible; however, such a condition appears to be met in the syntheses employing appropriately substituted acetophenones,<sup>9</sup> benzoic acids,<sup>10</sup> or bromobenzenes<sup>11</sup> as starting materials.

Pyridine-2-carbonyl chlorides are known to be difficult to prepare<sup>12</sup> and, in keeping with this behavior, we were unable to obtain the acid chloride of 1 in a pure state. However, reaction of the crude material (prepared from 1 and thionyl chloride) with the appropriate amine in dry benzene (or methylene chloride) was satisfactory for preparation of carboxamides 5a-e which showed the expected spectral properties (<sup>1</sup>H NMR, IR, MS) and gave acceptable ( $\pm 0.4\%$ ) values for CHN analyses.

Examination of 5a-d in the hot plate test for analgesia<sup>13</sup> and 5a,b for inhibition of phosphodiesterase<sup>14</sup> revealed no activity. However, in the rat adjuvant arthritis test<sup>15</sup> for antiinflammatory activity, 5a (at 30 mg/kg, po, for 5 days) showed 17% reduction in edema in 6/6 animals. This result is significant and appears to constitute a lead toward basic, nonsteroidal antiinflammatory agents derived from substituted pyridine-2-carboxamides.

### 3-Methyl-4-phenylpyridine (2)

A mixture of 10 ml of ethylene glycol, 3.3 ml (99 mmol) 95+ % hydrazine and 4.5 g (80 mmol) of potassium hydroxide was heated at 100° (oil bath temperature) and stirred vigorously until solution was achieved. A solution of 4.4 g (24 mmol) of crude 4-phenylpyridine-3-carboxaldehyde (4)<sup>8</sup> in ethylene glycol (7 ml) was then added dropwise while the temperature of the oil bath was slowly increased to the boiling point of the solution. When the addition was complete the stirred reaction mixture was heated under gentle reflux until gas evolution ceased, cooled, diluted with water (20 ml) and extracted with ether (3 x 30 ml). The combined ether extracts were extracted with water (2 x 90 ml) and dried over sodium sulfate. Evaporation of the solvent gave 3.6 g (89%) of essentially pure 2 as a tan oil. Its <sup>1</sup>H NMR spectrum, R<sub>f</sub> value and GC retention time were identical to those of an authentic sample<sup>2</sup> of 2. In a large scale run in which only crude intermediates were isolated, 1.0 mol of  $\alpha$ -methylstyrene afforded pure 2 in at least 75% overall yield after distillation: bp 104-106°C/0.3 mm [lit.<sup>2</sup> bp 96-98°C/0.2 mm].

### General Procedure for Preparation of Amides 5a-e.

To a well-stirred mixture of 320 mg (1.50 mmol) of 3-methyl-4-phenylpyridine-2-carboxylic acid prepared from 2 as previously described<sup>2</sup>, and anhydrous sodium carbonate (1.0 g) in dry benzene (15 ml) was added 0.19 ml (2.88 mmol) thionyl chloride in one portion. The reaction was then stirred and heated at reflux for 2.5 hr during which time the white solid which initially formed on addition of the thionyl chloride slowly dissolved. At the end of the reflux period the yellow solution was cooled below room temperature (ice bath) and a solution of 1.70-2.0 mmol of the amine in 15 ml of dry benzene or methylene chloride was added over ten minutes. Upon completion of the addition the stirred solution was refluxed for 2.0 hr, cooled to room temperature and 20 ml of water was added. The benzene layer was separated, washed with 2 x 20 ml of satur-

ated brine and dried with sodium sulfate. Evaporation of the solvent gave the crude amide as a oil which was then converted to the appropriate salt. Using this procedure the following amide salts were prepared in the yields indicated: 5a·HBr, mp 198° d, 72%; 5b·H<sub>2</sub>C<sub>2</sub>O<sub>4</sub>, mp 175° d, 75%; 5c·HBr, mp 270° d, 66%; 5d·CH<sub>3</sub>SO<sub>3</sub>H, mp 253° d; (5e)<sub>2</sub>·H<sub>2</sub>C<sub>2</sub>O<sub>4</sub>·H<sub>2</sub>O, mp 140-141° 62%. All of the above amide salts gave satisfactory elemental analyses and the IR spectra of the crude free amides show strong absorption at 1630-1640 cm<sup>-1</sup>.

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