3-SUBSTITUTED PYRIDINES. PREPARATION OF 3, 5-DIMETHYLPYRIDINE-4-PHENYLDIPYRIDINE, AND SYNTHESES BASED ON IT

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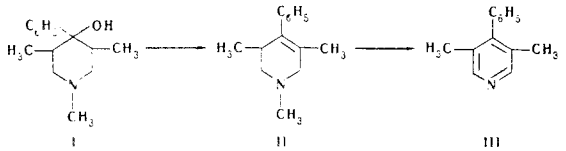
3, 5-Dimethyl-4-phenylpyridine is prepared by catalytic dehydrogenation and N-demethylation of 1, 3, 5-trimethyl-4-phenyl-Δ^3-piperidine. Oxidation of the former gives 4-phenylpyridine-3, 5-dicarboxylic acid and the dimethyl ester and bis(diethylamide) of the acid are prepared. The same acid is used to prepare 4-phenylpyridine, methyl 2-azafluorenone-4-carboxylate, and also a compound assumed to be 6, 14 dioxo-3-azatetracyclo[9.2.1.$0^{5,13}$.$0^{7,12}$]tetradeca-2, 4, 7, 9, 11, 13-hexaene.

In the authors' laboratory the preparation of substituted pyridine bases having the given structure has been studied, for a large number of cases, using dehydrogenation and N-dealkylation of the appropriate piperidine derivatives [1]. However, in all the syntheses so far effected, the subjects of investigation have been γ-substituted 2, 5-dimethylpiperidines, and similarly substituted Δ^4-tetrahydropyridines. That is because the accessible 1, 2, 5-trimethylpiperid-4-one [2], made on an industrial scale, offers greater possibilities for synthesizing γ-substituted 2, 5-dimethylpiperidines.

The present paper describes the synthesis of a dimethyl-substituted γ-phenylpyridine with the methyls differently disposed, 3, 5-dimethyl-4-phenylpyridine III.

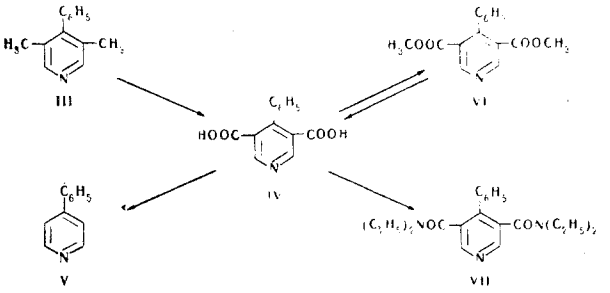
The starting compound for this synthesis was the previously described [3] 1, 3, 5-trimethyl-4-phenylpiperid-4-ol I. Sulfuric acid dehydration of the latter gave 1, 3, 5-trimethyl-4-phenyl-Δ^3-tetrahydropyridine II, and this was catalytically dehydrogenated and N-demethylated over the Mark K-12 industrial catalyst, at 400°–410° C, to give a 73% yield of 3, 5-dimethyl-4-phenylpyridine III.



I II III

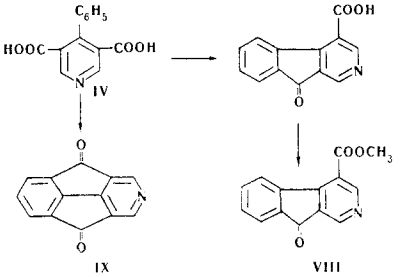
To prove the structure of 3, 5-dimethyl-4-phenylpyridine III, it was oxidized to 4-phenylpyridine-3, 5-dicarboxylic acid IV. Heating (240°–250° C) the latter with water in an autoclave led to complete decarboxylation to 4-phenylpyridine V [4]. From acid IV was prepared its dimethyl ester VI, and hydrochloric acid hydrolysis of the latter gave the hydrochloride of the starting acid IV.

Because pyridinecarboxamides usually exhibit specific physiological activity, and include some compounds with a tranquilizing action on the central nervous system, the bis(diethylamide) of 4-phenyl-pyridine-3, 5-dicarboxylic acid (VII) was made by treating acid IV with thionyl chloride, and then reacting the product with diethylamine.



III IV V VI VII

The substituted pyridine bases prepared in this laboratory, in particular 4-phenylpyridine-3, 5-dicarboxylic acid described, are of interest as starting materials for synthesizing condensed pyridine ring heterocyclic compounds. Cyclocondensation of this dibasic acid has been effected. Heating acid IV with sulfuric acid results in condensation involving not only one, but also two carboxyl groups simultaneously.



IV IX VIII

Two heteropolycyclic compounds were isolated: methyl 2-azafluorenone-4-carboxylate (VIII) and, in low yield, a compound assumed to be 6, 14-dioxo-3-azatetracyclo[9.2.1.$0^{5,13}$.$0^{7,12}$]tetradeca-2, 4, 7, 9, 11, 13-hexaene (IX).

EXPERIMENTAL

1, 3, 5-Trimethyl-4-phenyl-Δ^3-tetrahydropyridine (II). 24.6 g (0.11 mole) Of mixed isomeric 1, 3, 5-trimethyl-4-phenylpiperid-4-ols (I) (mp 106°–122° C) and 63.5 g 80% H_2SO_4 were heated together for 6 hr at 100° C. 115 ml water and 70 g Na_2CO_3 were added to the products, the organic bases extracted with ether, the extracts dried over Mg_2SO_4, and distilled, to give 18.7 g 1, 3, 5-trimethyl-4-phenyl-Δ^3-tetrahydropyridine (II), bp 93°–94° C (1 mm); n_D^{20} 1.5393, yield 82.8%. The hydrochloride was obtained treating the base II with a dioxane solution of HCl gas; mp 222.5°–223° C (ex EtOAc-MeOH). Found: N 6.09; 6.05%, calculated for $C_{14}H_{19}N \cdot HCl$: N 5.89%.

3, 5-Dimethyl-4-phenylpyridine (III). A solution of 20.1 g (0.1 mole) 1, 3, 5-trimethyl-4-phenyl-Δ^3-tetrahydropyridine (II) in 70 ml benzene was passed over 160 ml Mark K-12 catalyst, at a constant rate over a period of 4 hr. The catalyst zone temperature was 400°–410° C. 5.5 *l*

(732 mm, 22° C) gas was collected, the catalyzate dried over granulated KOH, and the solvent distilled off, to give 14.5 g crystalline precipitate, which was dissolved in hot heptane. The hot solution was run through an Al_2O_3 column, and 13.35 g crystals of 3, 5-dimethyl-4-phenylpyridine III crystallized out from the percolated solution, as colorless crystals, mp 85°–86° C, yield 73%. Found: N 7.80, 7.59%, calculated for $C_{13}H_{13}N$. N 7.65%.

4-Phenylpyridine-3, 5-dicarboxylic acid (IV). a) A mixture of 3 g (0.016 mole) 3, 5-dimethyl-4-phenylpyridine (III) and a solution of 11.4 g (0.069 mole) $KMnO_4$ in 280 ml water was refluxed and stirred for 4 hr. The MnO_2 was filtered off and washed a few times with hot water. The filtrate was partly evaporated, and then made acid to Congo Red with dilute (1:1) H_2SO_4. The precipitate was filtered off and recrystallized from water, to give 0.57 g IV, colorless crystals, mp 234°–236° C. Found: N 5.48; 5.48%, calculated for $C_{13}H_9NO_4$: N 5.77%.

b) 10.8 g (0.059 mole) 3, 5-Dimethyl-4-phenylpyridine III was oxidized similarly. After separating off the precipitate of MnO_2, the solution was made acid to Congo Red with HCl, and evaporated to dryness. 50 ml MeOH was added to the carefully dried residue, and the mixture refluxed for 6 hr, while dry HCl gas was passed in. The MeOH was vacuum distilled off at about 40° C. After cooling, 200 ml ice water was added, and the solution made strongly alkaline, with cooling, with Na_2CO_3 solution. The organic bases were extracted with ether. After drying with $MgSO_4$, the ether was distilled off to give pale yellow crystals, which were then dissolved in boiling heptane-EtOAc (10:1), and run through an alumina column under pressure. On cooling dimethyl 4-phenylpyridine-3, 5-dicarboxylate (VI) came down as colorless transparent crystals, mp 91°–93° C. It crystallized well from diethylamine, less well from water. Found: N 4.77, 4.90%, calculated for $C_{15}H_{13}NO_4$: N 5.17%.

c) 1.6 ml conc HCl was added to 1 g (3.7 mM) dimethyl ester VI, and the mixture gradually evaporated to dryness in a porcelain basin. Recrystallizing the residue (0.86 g) from EtOAc and then from water gave 4-phenylpyridine-3, 5-dicarboxylic acid hydrochloride, mp 184°–186° C. Found N 4.75; 4.80%, calculated for $C_{13}H_9NO_4$: N 5.01%.

4-Phenylpyridine (V). 0.5 g (2.1 mM) IV and 5 ml water were autoclaved for 3 hr at 240°–250° C. The oil formed was separated off and and dissolved in ether. The water layer was extracted a few times with ether, and the ether extract dried over KOH. Distilling off the ether gave 0.23 g 4-phenylpyridine V, with mp 74°–76° C after recrystallizing from water, undepressed mixed mp with a known specimen.

N, N-diethyl-4-phenylpyridine-3, 5-dicarboxamide (VII). 12 ml $SOCl_2$ was added gradually, over a period of 30 min, to 8 g (0.033 mole) acid IV, and the mixture refluxed for 5 hr. After distilling off excess $SOCl_2$, the residue was cooled, and 17 ml Et_2N added, after which the whole was heated on a steam bath for 5 hr. Excess amine was distilled off, 200 ml ice water added, and the solution neutralized with cooling, by means of 50% KOH. The mixture was extracted 8 times with ether. The ether extract gave 3.1 g dicarboxamide VII, mp 132°–133° C (ex petrol ether). Found: C 71.13; 71.37; H 7.46; 7.23; N 11.61; 11.73%, calculated for $C_{21}H_{27}N_3O_2$: C 71.39; H 7.65; N 11.89%.

Methyl 2-azafluorenone-4-carboxylate (VIII) and **6,14-dioxo-3-azatetracyclo[9. 2. 1. $0^{5,13}$. $0^{7,12}$]tetradeca-2, 4, 7, 9, 11, 13-hexaene (IX).** 4 g 4-phenylpyridine-3, 5-dicarboxylic acid IV and 15 ml conc H_2SO_4 were heated together for 5 hr on a steam bath. After cooling the products were diluted with 100 ml water, neutralized with Na_2CO_3, and extracted with ether. After drying with $MgSO_4$, the ether extracts gave 0.04 g orange crystals mp 132°–134° C (ex petrol ether). Analytical data, physical properties, and the method of isolation indicated that they were the tetracyclic compound IX. Found: N 6.55; 6.83%, calculated for $C_{13}H_5NO_2$: N 6.75%.

After extracting with ether the aqueous solution was acidified with HCl, evaporated, and carefully dried. 80 ml dry MeOH was added to the residue, and the mixture refluxed for 6 hr while dry HCl was passed in. The MeOH was distilled off, the residue made alkaline, and extracted with ether to give a crystalline residue (2 g). Recrystallization from petrol ether and then from water gave 1.8 g VI dimethyl ester, mp 91.5°–93° C, and 0.01 g bright yellow crystals of VIII, mp 195°–197° C. Found N 5.35; 5.49%, calculated for $C_{14}H_9NO_3$: N 5.85%.

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