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AROMATIZATION OF N-SUBSTITUTED PIPERIDINE COMPOUNDS

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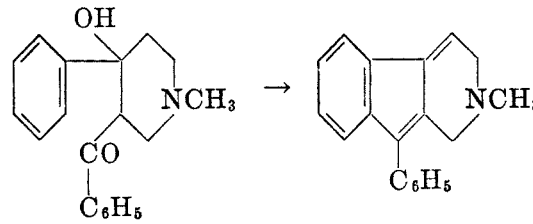
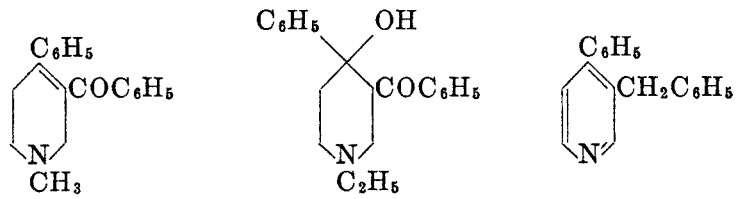
In a previous paper (1) a procedure was described by which 1-pyridindene derivatives could be obtained by the action of hydrobromic and sulfuric acid on several piperidine derivatives. In the special case of 1-methyl-3-benzoyl-4-hydroxy-4-phenylpiperidine (I) the reaction yields 2-methyl-9-phenyl-2,3-dihydro-1-pyridindene (II). It was logical to initiate a study of other dehydrating agents in this reaction, and as a first approach an investigation of the action of acetic anhydride was undertaken.



I II

It was noted earlier (2) that 1-methyl-3-benzoyl-4-phenyl-4-acetoxypiperidine was obtained in excellent yield by the reaction of I with acetic anhydride at room temperature in the presence of a catalytic amount of sulfuric acid. The acetoxy base can be distilled without decomposition in the presence of a small amount of potassium carbonate.

The reaction with acetic anhydride took a different course when the temperature was raised to 90–100°. In this case a compound was isolated in about 15% yield, the analysis of which is in agreement with formula III.



III IV V

The position of the double bond was not rigidly established, but it is very likely that it is in the position indicated, since this position is associated with maximum conjugation.

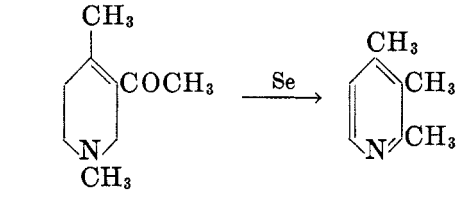
When, instead of isolating compound III, the reaction mixture was distilled under reduced pressure an unexpected reaction took place. A product of formula $C_{18}H_{15}N$, which can be isolated as an oxalate or hydrobromide, was obtained in about 30–35% yield. The neutral equivalent of the oxalate was abnormally low,

indicating a combination of the base and oxalic acid in the molecular ratio of 2:3 respectively. The free base on titration with hydrochloric acid showed the properties of a very weak base. It was suspected that the new compound was a pyridine derivative instead of a piperidine derivative. This assumption was supported by the finding that the corresponding N-ethyl derivative (IV) (3) under the same conditions gave the identical product as the N-methyl derivative (I). Obviously, then, the substituent on the nitrogen atom in the original piperidine bases must have been lost in the treatment with acetic anhydride. The unknown reaction product was hydrogenated catalytically, yielding a base which reacted with *p*-nitrobenzoyl chloride to give a *p*-nitrobenzoyl derivative. This finding indicated that a hydrogen atom was attached to the nitrogen in the hydrogenated product.

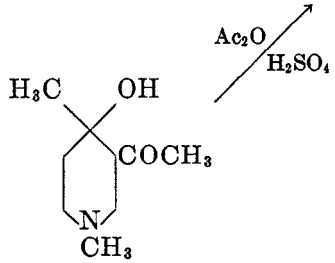
The unknown weak base was converted into the quaternary derivative with methyl *p*-toluenesulfonate, and the methyl *p*-toluenesulfonate was hydrogenated catalytically. A considerably stronger base than the original one resulted. It was possible to titrate this base with hydrochloric acid in the normal manner. From the analysis of the unknown weak base and from the properties just reported, it is possible to derive a preliminary formula containing a pyridine ring, two phenyls, a carbon, and two hydrogens.

The simple assumption that these fragments were fitted together as in V and that no change in original skeletal structure had occurred was not in agreement with the resistance of the substance to oxidation. It was largely unchanged after it had been boiled for 40 minutes with excess chromic oxide in acetic acid (56% recovered) or with excess potassium permanganate in pyridine for 9 hours (75% recovered).

In search for similar cases, the work of Prelog, Komzak, and Moor (4) came to our attention. These authors had subjected the unsaturated compound (VI) to the action of selenium and obtained 2,3,4-trimethylpyridine (VII).

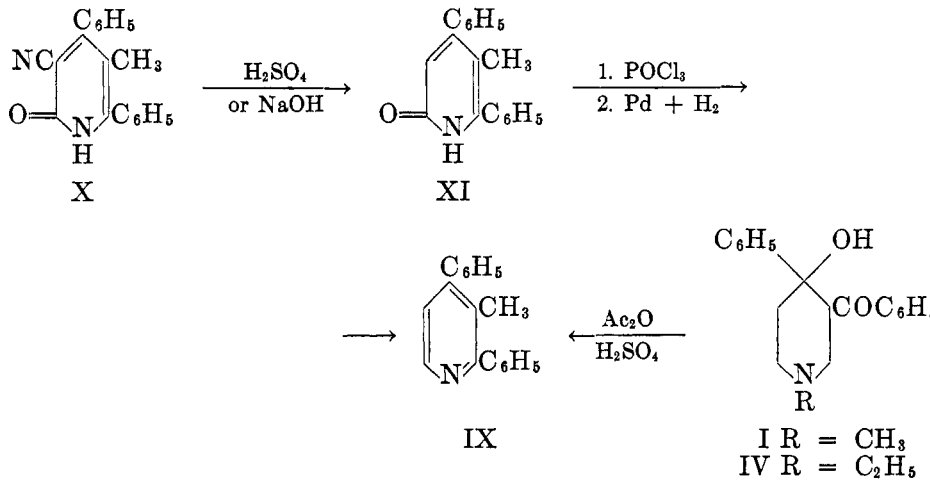


VI VII



VIII

These results and the difficulty of oxidation led us to suspect that our unknown pyridine derivative was in reality 2,4-diphenyl-3-methyl-pyridine (IX). To decide this question compound IX was synthesized by an unambiguous method. The starting material 3-cyano-4,6-diphenyl-5-methyl-2-pyridone (X) was synthesized according to the procedure of Basu (5) by the reaction of methyldibenzoylmethane and cyanoacetamide. Hydrolysis and decarboxylation with 80% sulfuric acid or aqueous alkali (6) gave the pyridone (XI), for which the melting point 228–229° was found instead of 263–264° as reported by Basu. When saponification was effected by aqueous alkali, 3-carboxy-4,6-diphenyl-5-methyl-2-pyridone could also be obtained. Treatment of XI with phosphorus oxychloride gave the chloro derivative which yielded the desired 2,4-diphenyl-3-methyl-pyridine (IX) on catalytic hydrogenation. This compound proved indeed to be identical with the weak base resulting from the acetic anhydride treatment of the original piperidine bases (I) and (IV).



It is important to point out a significant difference between the aromatizations in the case of Prelog's compound (VII) and our compound (IX). The Swiss workers started with a tetrahydropyridine derivative (VI), whereas the starting material for our investigation is the 4-hydroxypiperidine (I or IV). The Swiss workers utilized selenium and indicated that a dehydrogenation was involved, whereas in our case acetic anhydride and sulfuric acid were used.

It seemed likely that Prelog's compound (VII) could be obtained directly by starting with the corresponding 4-hydroxy compound (VIII), which Prelog and his group utilized as a starting material for the preparation of their tetrahydropyridine (VI). This was indeed found to be the case. Treatment with acetic anhydride and sulfuric acid was sufficient to bring about the desired aromatization.

From this discussion it may appear that an acid catalysis is responsible for the formation of the pyridine derivatives with the intermediate formation of unsaturated compounds. The situation, however, seems to be more complicated,

since it was found that when the unsaturated ketone (VI) was distilled slowly over a small amount of sulfuric acid without acetic anhydride the pyridine derivative (VII) could not be isolated. It may be possible that an acetoxy derivative is involved in the aromatization.

This new type of aromatization may prove useful in the preparation of certain pyridine derivatives.

EXPERIMENTAL

All melting points are uncorrected.

PART I. REACTION OF 1-METHYL-3-BENZOYL-4-HYDROXY-4-PHENYLPIPERIDINE (I) WITH ACETIC ANHYDRIDE AND SULFURIC ACID

A. *1-Methyl-3-benzoyl-4-phenyl-1,2,5,6-tetrahydropyridine* (III). A mixture of 147 g. of 1-methyl-3-benzoyl-4-hydroxy-4-phenylpiperidine (I), 870 cc. of acetic anhydride, and 30 drops of concentrated sulfuric acid was placed on a steam-bath for 2.5 hours and shaken occasionally. The solvent was removed at the water pump in a bath which was gradually raised to 95°. To the residue 550 cc. of water and 500 cc. of ether were added, and the mixture was neutralized with about 140 g. of sodium carbonate below 30°. Three layers were obtained. The lowest layer was separated and discarded. To the remainder 140 cc. of water was added, the mixture was shaken, and the ether layer was separated. The ether layer was shaken with 70 cc. of 10% sodium carbonate and twice with 150 cc. of water, dried with sodium sulfate, and treated with an ethereal solution of oxalic acid until no further precipitate was obtained. Crystallization of the precipitate from 1700 cc. of ethanol gave 28 g. of the *oxalate* of 1-methyl-3-benzoyl-4-phenyl-1,2,5,6-tetrahydropyridine (III), m.p. 162–165°.

Anal. Calc'd for $C_{19}H_{19}NO \cdot C_2H_2O_4$: C, 68.65; H, 5.76.
Found: C, 68.59; H, 5.82.

Base. The base was obtained from a solution of the oxalate in dilute alcohol by treatment with alkali. After crystallization from dilute alcohol, the base melted at 95–96°.

Anal. Calc'd for $C_{19}H_{19}NO$: C, 82.28; H, 6.90.
Found: C, 82.51; H, 6.75.

Hydrochloride. This compound was prepared by the passage of hydrogen chloride into a solution of the base in ether. It melted at 194–195°.

B. *2,4-Diphenyl-3-methylpyridine* (IX). A mixture of 500 g. of 1-methyl-3-benzoyl-4-hydroxy-4-phenylpiperidine (I), 2500 cc. of acetic anhydride, and 87 drops of concentrated sulfuric acid was warmed on the steam-bath for 2.5 hours. The mixture was distilled first at the water pump and then at an oil pump provided with a large trap cooled with acetone and solid carbon dioxide. Evolution of some very volatile material occurred just before distillation of the main fraction. Caution should be exercised at this point, and the source of heat should be removed until the evolution has subsided. Continued distillation gave 244 g. of an oil boiling at 180–195° at 1.3 mm. The oil solidified on seeding with a previously prepared sample of 2,4-diphenyl-3-methylpyridine (IX).

Hydrobromide. The crude pyridine derivative was warmed to solution with 976 cc. of 48% hydrobromic acid, and the solution was poured into about 2 l. of water. The crystals of hydrobromide thus obtained weighed 180 g. and melted at 238–241°. The substance may be purified by crystallization from ethanol.

Anal. Calc'd for $C_{18}H_{15}N \cdot HBr$: C, 66.3; H, 4.9; Br, 42.5.
Found: C, 66.6; H, 4.5; Br, 24.5.

Oxalate. The crude base was dissolved in ether and treated with an ethereal solution of oxalic acid until no further precipitate was obtained. After crystallization from ethanol, the pure oxalate, m.p. 173–175°, was obtained.

Anal. Calc'd for $2\ C_{18}H_{15}N \cdot 3\ C_2H_2O_4$: C, 66.31; H, 4.77; N, 3.68; Neut. equiv., 127.
Found: C, 66.23; H, 4.97; N, 3.52; Neut. equiv., 129.

Base. The base can be obtained from the pure oxalate or hydrobromide by the action of alkali followed by distillation and crystallization from Skellysolve C or dilute alcohol. The pure substance melts at 60–61°. On electrometric titration with dilute hydrochloric acid no sharp point of inflection was noted.

Anal. Calc'd for $C_{18}H_{15}N$: C, 88.13; H, 6.16; N, 5.71.
Found: C, 87.84, H, 6.40; N, 5.47.

Hydrochloride. The hydrochloride melted over the range 219–226° after crystallization from alcohol-ether.

Anal. Calc'd for $C_{18}H_{15}N \cdot HCl$: C, 76.72; H, 5.72; Cl, 12.6.
Found: C, 76.97; H, 5.91; Cl, 12.6.

Methiodide. The methiodide was obtained when a solution of 10 g. of the base and 10 cc. of methyl iodide in 100 cc. of benzene was allowed to stand for 5 days. A yield of 6.9 g. was obtained. The compound melts at 221° with some preliminary softening at about 214°.

PART II. 2,4-DIPHENYL-3-METHYLPYRIDINE FROM THE REACTION OF 1-ETHYL-3-BENZOYL-4-HYDROXY-4-PHENYLPIPERIDINE (IV) WITH ACETIC ANHYDRIDE AND SULFURIC ACID

A mixture of 58 g. of 1-ethyl-3-benzoyl-4-hydroxy-4-phenylpiperidine (IV), 290 cc. of acetic anhydride, and 10 drops of sulfuric acid was treated as in Part I (B). At 185–200° and 0.9 mm., 23.5 g. of oil distilled over. On solution in ether and treatment with an ethereal solution of oxalic acid 21 g. of precipitate was obtained. After crystallization from ethanol, 14.2 g. of the oxalate of 2,4-diphenyl-3-methylpyridine was obtained, as indicated by the neutral equivalent of 132. A sample of the oxalate was converted into the base, m.p. 60°. The hydrobromide melted at 239–241°. The hydrochloride melted at 219–226°. Neither the base, the hydrobromide, nor the hydrochloride gave a depression in melting point when each was mixed with the corresponding substance from Part I (B).

PART III. OXIDATION OF 2,4-DIPHENYL-3-METHYLPYRIDINE (IX)

When 2 g. of 2,4-diphenyl-3-methylpyridine (IX) was refluxed for 40 minutes with 3 g. of chromium oxide in acetic acid, 1.69 g. (56%) of unchanged material was isolated as the oxalate. Heating of 1 g. of IX with 5 g. of potassium permanganate in boiling pyridine left the compound unchanged, 0.75 g. of starting material (75%) being recovered.

PART IV. HYDROGENATION EXPERIMENTS WITH 2,4-DIPHENYL-3-METHYLPYRIDINE (IX)

1-p-Nitrobenzoyl-2,4-diphenyl-3-methylpiperidine. A mixture of 1.23 g. of 2,4-diphenyl-3-methylpyridine, 0.20 g. of platinum oxide catalyst, 15 cc. of *N* hydrochloric acid, and 165 cc. of ethanol was hydrogenated at room temperature during a period of 1.5 hours and then at 55° for 5.5 hours. After removal of the catalyst and evaporation of the solvent, the residue was dissolved in 15 cc. of water and 25 cc. acetone. The mixture was made alkaline with 5 cc. of 10% sodium hydroxide and then treated alternately with *p*-nitrobenzoyl chloride and 10% sodium hydroxide. In this manner 3.0 g. of the chloride and 7 cc. of 10% sodium hydroxide were utilized for the reaction. The mixture was evaporated to dryness on the steam-bath, and the residue was extracted with dilute hydrochloric acid and ether. The ether solution was evaporated to dryness, and the residue was digested with Skellysolve B. In this manner 0.11 g. of the *p*-nitrobenzamide, m.p. 146–148°, was obtained. Crystallization from ethanol gave the pure product, m.p. 151–153°.

Anal. Calc'd for $C_{25}H_{24}N_2O_3$: C, 74.98; H, 6.04.
Found: C, 75.04; H, 5.93.

B. *1,3-Dimethyl-2,4-diphenyl-piperidine.* 1. *Quaternary salt.* A mixture of 24.5 g. of 2,4-diphenyl-3-methylpyridine and 18.6 g. of methyl *p*-toluenesulfonate was heated for 15 minutes at 160° and then dissolved in 160 cc. of ethanol.

2. *Hydrogenation.* The above solution was hydrogenated in the presence of 1.0 g. of platinum oxide catalyst at about 50 p.s.i. during about 2 hours at 50–70°. Very little hydrogen was absorbed, and it was necessary to add a fresh charge of catalyst on two separate

occasions in order to increase the rate of hydrogen absorption. Approximately 3.5 moles of hydrogen were absorbed during a total period of about 10 hours. After filtering the catalyst, the solution was treated with dilute alkali and allowed to crystallize overnight. In this manner 7.3 g. of almost pure 1,3-dimethyl-2,4-diphenylpiperidine was obtained. Crystallization from alcohol gave the pure product, m.p. 101–103°. On electrometric titration with standard acid a curve with a rather sharp point of inflection was obtained.

Anal. Calc'd for $C_{19}H_{23}N$: C, 85.99; H, 8.73; Neut. equiv., 265.

Found: C, 86.09; H, 9.06; Neut. equiv., 270.

The hydrochloride after crystallization from ethanol melted at 256–258°.

PART V. ALTERNATIVE SYNTHESIS OF 2,4-DIPHENYL-3-METHYLPYRIDINE (IX)

A. *3-Cyano-4,6-diphenyl-5-methyl-2-pyridone* (X). This compound was prepared essentially according to Basu (5) by refluxing 13.2 g. of methyldibenzoylmethane, 2.4 g. of piperidine, and 100 cc. of ethanol for about 12 hours. Yield 6.4 g., m.p. 295–298°.

B. *4,6-Diphenyl-5-methyl-2-pyridone* (XI). 1. *With sulfuric acid.* A mixture of 2.32 g. of the cyano compound (X), 9 cc. of water, and 18 cc. of sulfuric acid was refluxed for 1 hour. The mixture was poured into water and filtered. The precipitate was crystallized from ethanol to give 0.53 g. of 4,6-diphenyl-5-methyl-2-pyridone, m.p. 227–229°. Basu (5) reported a melting point of 263–264° for the same compound.

Anal. Calc'd for $C_{18}H_{15}NO$: C, 82.7; H, 5.8; N, 5.4.

Found: C, 82.5; H, 6.2; N, 5.4.

2. *With alkali.* A mixture of 6.4 g. of 3-cyano-4,6-diphenyl-5-methyl-2-pyridone (X), 58 cc. of *N* sodium hydroxide, and 40 cc. of water was placed in an autoclave at 160° for 113 hours according to a previously published procedure (6). Acidification to *p*H 9.5 gave 4.7 g. of 4,6-diphenyl-5-methyl-2-pyridone, m.p. 226–227°. After crystallization from alcohol, it melted at 228–229°.

Anal. Calc'd for $C_{18}H_{15}NO$: C, 82.7; H, 5.8.

Found: C, 82.8; H, 5.8.

3. *3-Carboxy-4,6-diphenyl-5-methyl-2-pyridone.* A mixture of 1.46 g. of 3-cyano-4,6-diphenyl-5-methyl-2-pyridone (X), 25 cc. of water, and 13 cc. of *N* sodium hydroxide was heated in an autoclave at 160° during a period of about 42 hours. On addition of water 0.43 g. of crude 4,6-diphenyl-5-methyl-2-pyridone (X), m.p. 216–218°, was obtained. Acidification to *p*H 6.7 gave 0.10 g. of solid, m.p. 251–270°, whose identity was not established. Further acidification to *p*H 1.7 gave 0.80 g. of 3-carboxy-4,6-diphenyl-5-methyl-2-pyridone. The pure compound, m.p. 270–271°, was obtained by crystallization from methanol.

Anal. Calc'd for $C_{19}H_{15}NO_3$: C, 74.7; H, 4.9.

Found: C, 74.7; H, 4.6.

4. *2-Chloro-4,6-diphenyl-5-methylpyridine.* A mixture of 2.0 g. of 4,6-diphenyl-5-methyl-2-pyridone (XI) and about 5 cc. of phosphorus oxychloride was heated in a sealed tube at 200° for 2 hours. The mixture was poured into ice and neutralized with 10% sodium carbonate. The precipitate thus obtained was crystallized from ethanol. A yield of 1.6 g. of 2-chloro-4,6-diphenyl-5-methylpyridine, m.p. 92–93°, was obtained.

Anal. Calc'd for $C_{18}H_{14}ClN$: C, 77.28; H, 5.04.

Found: C, 76.84; H, 5.03.

5. *2,4-Diphenyl-3-methylpyridine* (IX). A mixture of 0.80 g. of 2-chloro-4,6-diphenyl-5-methylpyridine, 0.30 g. of palladium chloride, 2.0 g. Merck's activated charcoal, 20 cc. of *N* hydrochloric acid, and methanol to make a volume of 165 cc. was hydrogenated under a pressure of 120–190 cm. of mercury during 2 hours. The catalyst was filtered and the filtrate evaporated *in vacuo* to dryness. The residue was dissolved in water, treated with dilute alkali, and extracted with ether. After drying with sodium sulfate and evaporation of the ether, a solid residue was obtained. Crystallization from 4 cc. of Skellysolve B gave 0.45 g. of 2,4-diphenyl-3-methylpyridine (IX), m.p. 59–60°. No depression was obtained in the melting point when either the base or methiodide was mixed with the corresponding material from Part I (B). The hydrochloride and hydrobromide melted respectively at

218–223° and 236–238°, corresponding with the melting points of the hydrochloride and hydrobromide of 2,4-diphenyl-3-methylpyridine. The absorption spectrum of the base was practically identical with the base from Part I (B).

PART. VI EXPERIMENTS WITH 1,4-DIMETHYL-3-ACETYL-4-HYDROXYPIPERIDINE AND DERIVATIVES (VIII)

A. *2,3,4-Trimethylpyridine* (VII). A mixture of 36 g. of a mixture of the α and β stereoisomeric forms of 1,4-dimethyl-3-acetyl-4-hydroxypiperidine (VIII), 180 cc. of acetic anhydride, and 6 drops of sulfuric acid was heated on the steam-bath for 2.5 hours. Most of the excess acetic anhydride was distilled through a 12-plate column at about 10 mm. The residue was then distilled at ordinary pressure. A fraction, boiling at 174–178° and weighing 12.9 g., was collected. To an ether solution of this material a solution of picric acid in ether was added. In this manner 20.6 g. of picrate, m.p. 158–160°, was obtained. Crystallization from methanol gave 16.9 g. of the pure picrate of 2,3,4-trimethylpyridine (VII), m.p. 160–163°. The picrate was steam-distilled in the presence of 100 cc. of 50% potassium carbonate. The distillate was extracted with ether and the ether solution dried and distilled to give an oil boiling at 180–185°; $n^{24.7}_{D}$ 1.5127; d^{23}_{25} 0.952. The picrolonate after crystallization from methanol melted at 235–237°d. All of the above properties agree with those reported by Prelog, Komzak, and Moor (4).

B. *Distillation of 1,4-dimethyl-3-acetyl-1,2,5,6-tetrahydropyridine* (VI) *with sulfuric acid*. The tetrahydropyridine (VI) was prepared according to the method of Prelog and Komzak (7). A mixture of 9.73 g. of this material and 2 drops of sulfuric acid was distilled slowly at ordinary pressure. A fraction weighing 2.8 g. was collected below 100°. It had the strong odor of an amine. On continued distillation the temperature rose rapidly up to 270°. No material boiling in the range of 2,3,4-trimethylpyridine was noted.

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SUMMARY

1-Alkyl-3-benzoyl-4-hydroxy-4-phenylpiperidines undergo rearrangement on treatment with acetic anhydride and sulfuric acid into 2,4-diphenyl-3-methylpyridine. The same type aromatization also occurs with 1,4-dimethyl-3-acetyl-4 hydroxypiperidine.

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