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REDUCTION PRODUCTS DERIVED FROM α-PHENACYLPYRIDINE[1]

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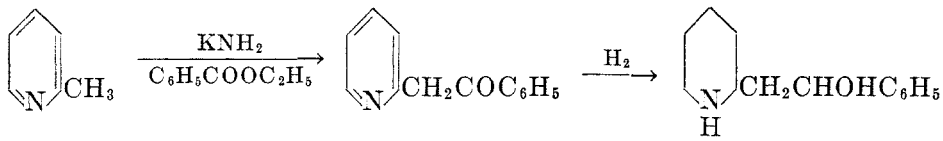
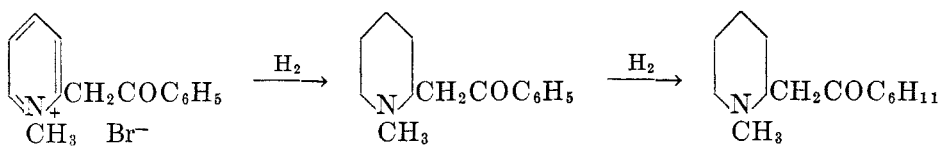
α-Phenacylpyridine (I), originally synthesized from α-picoline by a series of steps (1, *cf.* 2), has recently been obtained from this starting material in essentially a single operation (3, 4, 5). In the present work, I was conveniently prepared (6) by adding α-picoline and ethyl benzoate in that order to a solution of potassium amide in liquid ammonia.



I II

The catalytic reduction of I to 2-(β-hydroxy-β-phenylethyl)piperidine (II) had previously been reported by Scheuing and Winterhalder (2). In our experience, the reduction of I (using either platinum oxide or Raney nickel catalyst) gave the two racemic forms of II melting at 112.5° and 98.5° respectively [the carbinol, m.p. 85°, described in the literature (2) is apparently a mixture].

The platinum oxide-catalyzed reduction (terminated when the calculated amount of hydrogen had been absorbed) of α-phenacylpyridine methobromide (III) gave 1-methyl-2-phenacylpiperidine (IV)[2] in good yield.[3]



III IV V

[1] The work described in this paper was done under a Contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the California Institute of Technology (E. R. Buchman, responsible investigator).

Prof. J. P. Wibaut has made valuable comments regarding the manuscript; it is a pleasure to acknowledge his kind interest.

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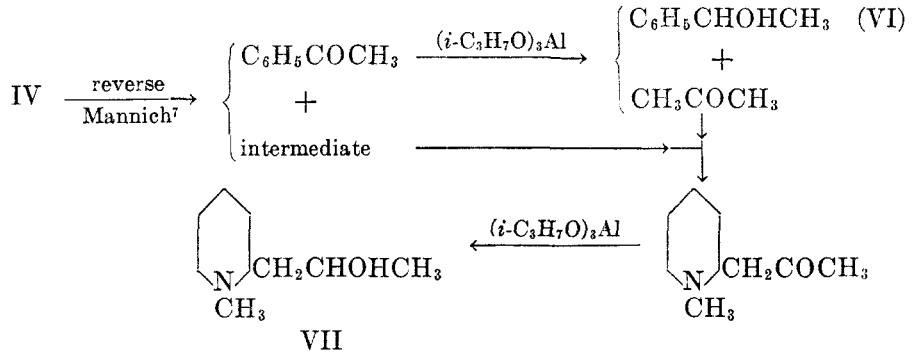
[2] Wieland and Ishimasa (7) isolated a minor lobelia alkaloid for which they suggested the structure N-methyl-II (dihydro-IV); they oxidized this carbinol to the corresponding ketone whose hydrochloride monohydrate melted at 109°; whether either of these compounds was optically active was not disclosed. Our racemic ketone (IV) gave an anhydrous hydrochloride, m.p. 172–173° dec.

[3] Compare conversion of α-acetonylpyridinemethosulfate (8) and of α,α′-diphenacylpyridine metho-*p*-toluenesulfonate (2) to the corresponding piperidine derivatives.

When the reduction was continued, hydrogen was taken up at a slower rate; there was isolated (in addition to IV) a compound tentatively formulated (on the basis of analytical results) as V.[4]

An attempted aluminum isopropoxide reduction[5] of IV gave a variety of products, among them phenylmethylcarbinol (VI) and, with reasonable certainty, 1-methyl-2-(β-hydroxypropyl)piperidine (VII)[6] [mixture of racemates (13a)]. The chart provides an explanation of the formation of these substances.



EXPERIMENTAL[8]

α-Phenacylpyridine (I). To a potassium amide solution [from 63 g. (1.6 gram-atoms) of potassium, *ca.* 1 l. of liquid ammonia, and ferric chloride catalyst] was added with stirring 80 g. (0.86 mole) of α-picoline (six minutes); to the resulting deep-red solution was added 220 g. (1.46 moles) of ethyl benzoate (eight minutes). A brick-yellow suspension formed which, during twenty minutes of stirring, lightened in color to lemon-yellow. The suspension was then diluted with 500 ml. of ether and agitation was continued for six hours (mixture warmed to room temperature) during which time ether was added to facilitate stirring. After treatment with a solution of 85 g. (1.6 moles) of ammonium chloride in 500 ml. of water (foaming!), the dark-green organic layer was separated, the aqueous phase was extracted with ether, and the combined ether extracts were extracted in turn with 1.2 l. of 1 *N* hydrochloric acid. The acid extract was then neutralized with excess potassium car-

[4] This observation is in marked contrast to the reported (2) smooth conversion of α,α′-diphenacylpyridine metho-*p*-toluenesulfonate to lobelanidine [1-methyl-2,6-di-(β-hydroxy-β-phenylethyl)piperidine]. The catalytic reduction of lobelia alkaloid analogs of IV has been little studied, *cf.* the reduction (9) of lobinin and of isolobinin. Note that Wibaut and co-workers (10) were able to effect the reduction of α-acetonylpyridine to 2-acetonylpiperidine.

[5] The aluminum isopropoxide reduction of Mannich ketones has seldom proved satisfactory (11).

[6] Wieland and Dane (12) have suggested the formula VII for a minor lobelia alkaloid, m.p. 85–87°. Our VII mixture was an oil, as were also previously reported (13) VII preparations. VII has been prepared by reduction of 1-methyl-2-acetonylpiperidine (13a), reduction of α-(β-hydroxypropyl)-pyridine methosulfate (13b), and methylation of mixed 2-(β-hydroxypropyl)piperidine racemates (13c).

[7] Compare the facile elimination of acetophenone from similarly constituted lobelia alkaloids (14).

[8] All melting points are corrected; microanalyses by Dr. G. Oppenheimer and staff of this Institute and by Huffman Microanalytical Laboratories, Denver, Colorado; spectral measurements by Miss P. Baskett and Mrs. M. Howton.

bonate and extracted with ether. The extracts were dried and distilled; the fraction b.p. 138–150° at 0.5 mm. [lit. (2) gives I, b.p. *ca.* 159° at 1 mm.] crystallized. This product (112 g.) contained benzamide; it was dissolved in 1 l. of acetone and treated with 65 ml. of 48% hydrobromic acid, giving a colorless precipitate of *I hydrobromide*, m.p. 142–147°, yield 105 g. (44% based on α-picoline). This salt crystallized from isopropyl ether-ethanol in colorless, rhombic plates, m.p. 157.2–157.9° [lit. (15) m.p. 156–157°], absorption spectrum (Fig. 1), approximate values of $\lambda_{max.}$ (aqueous solution) 255 mμ, 395 mμ (plateau). *I (free base)*, yellow needles from *n*-hexane-ether, m.p. 59.1–60.7° [lit. m.p. 50–51° (1); 59° (2, 3); 56° (4); 54° (5)] deteriorating rapidly on standing [*cf.* however (5)]; the absorption spectrum (*n*-hexane solution) is given in Fig. 1 [$\lambda_{max.}$ at 233 mμ, (254 mμ), (264 mμ), 300 mμ (plateau), 343 mμ]. A freshly prepared ethanolic solution of I exhibited three prominent maxima corresponding in position to those found in *n*-hexane but the spectrum was changing at such a rate that reproducible readings could not be obtained; the spectrum of the

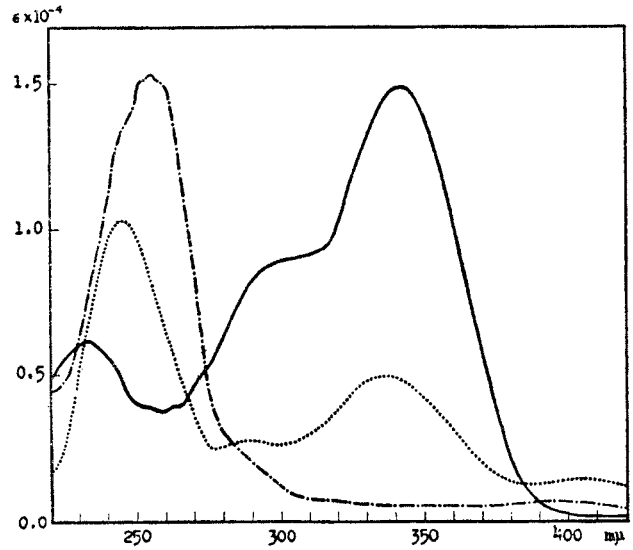


FIG. 1. ULTRAVIOLET ABSORPTION SPECTRA

——— α-Phenacylpyridine in *n*-hexane
..... α-Phenacylpyridine in 95% ethanol (solution one day old)
—·—·— α-Phenacylpyridine hydrobromide in water

ethanol solution after standing one day (not appreciably different from that of the same solution nine days later) is given in Fig. 1 ($\lambda_{max.}$ at 245 mμ, 289 mμ, 337 mμ, 404 mμ); note that this curve is in some respects intermediate between that found for I (in *n*-hexane) and that for I hydrobromide. *I oxime* melted at 116° [lit. m.p. 120° (2), 118° (16)]. *I picrate* crystallized from acetonitrile in sparse clusters of yellow, rectangular bars, some tubular, others tubes with a longitudinal opening down one face, m.p. 181.8–182.3° [lit. m.p. 176–177° (1); m.p. 179–180° (5)].

2-(β-Hydroxy-β-phenylethyl)piperidine (II). In a typical experiment, 27.7 g. of I hydrobromide, 75 ml. of ethanol, and 1 g. of Adams' platinum oxide catalyst were shaken with hydrogen at room temperature and atmospheric pressure. After thirty-one hours, the uptake was negligible and about 13.5 l. of gas had been absorbed (theory *ca.* 10.4 l.). The catalyst was filtered off and washed with ethanol; the filtrates, after evaporation to *ca.* 100 ml. and after two days in the ice-box, deposited 1.2 g. of crude α-II hydrobromide, m.p. 149–153°. Mother liquors were freed of solvent and treated with 50 ml. of acetone yielding a second crop of crystals (6.2 g)., m.p. 142°. A third crop (4.0 g.), m.p. *ca.* 134° was obtained

by again evaporating mother liquors, dissolving the residue in 25 ml. of butanone, and adding 18 ml. of isopropyl ether. A further similar treatment of the mother liquors using 15 ml. each of butanone and isopropyl ether gave 4.2 g. of hygroscopic material, m.p. *ca.* 111°. Basification of the final mother liquors gave crystalline, non-homogeneous material (4.6 g.).

A sample of crude α-II hydrobromide, m.p. 142–146°, after three recrystallizations from acetone-ethanol, had a constant m.p. 156.4–157.0°, clusters of very thin colorless blades with bluntly-pointed ends; this salt (SN 10,094) exhibited no activity when tested against avian malaria (17).

Anal. Calc'd for $C_{13}H_{19}NO \cdot HBr$: C, 54.55; H, 7.04; N, 4.89.
Found: C, 54.83; H, 7.14; N, 4.76.

The free base (α-II) was liberated from recrystallized hydrobromide and recrystallized from ligroin-isopropyl ether, sparsely-clustered colorless bars, m.p. 112.0–112.5°, analysis below. β-II was obtained from the hygroscopic mixed hydrobromides, m.p. *ca.* 111° (see above); this material was recrystallized, first by dissolving in acetone and diluting with ether and then from acetone-ethanol; basification of the mother liquors from the second recrystallization followed by five recrystallizations from 60–70° petroleum ether gave pure β-II, plates, m.p. 97.8–98.5°.

Anal. Calc'd for $C_{13}H_{19}NO$: C, 76.02; H, 9.33; N, 6.82.
Found (α-II): C, 76.16; H, 9.70; N, 6.63.
(β-II): C, 76.20; H, 9.80; N, 6.84.

The *picrates* of both forms of II were oils. Treatment of β-II with 48% hydrobromic acid under mild conditions (removal of excess acid *in vacuo*) resulted in replacement of the hydroxyl group; the product was a crystalline solid, colorless rectilinear plates from ethanol-water, m.p. 186–187° dec. (dependent on rate of heating).

Anal. Calc'd for $C_{13}H_{18}BrN \cdot HBr$: C, 44.72; H, 5.49; N, 4.01.
Found: C, 44.95; H, 5.45; N, 3.95.

An autoclave, charged with 20 g. of I (containing benzamide), 150 ml. of dioxane, 11 ml. of Raney nickel paste, and hydrogen at 140 atmospheres pressure, was heated for five hours at 85–145°. Distillation gave a mixture of oil and crystals, b.p. 100–145°/1 mm. [lit. (2) b.p. of II, 165°/4 mm.] The crystalline portion was recrystallized from benzene, m.p. 186–187°, analysis for $C_7H_{13}NO$; hexahydrobenzamide is reported (18) to melt at 184°, 185–186°. The oily portion crystallized on standing; 5 g. of this material was dissolved in 5 ml. of benzene; on cooling crude α-II separated, identified (after recrystallization from ligroin-benzene) by m.p. and mixture m.p. of the free base and of its hydrobromide. On further standing, the benzene mother liquors deposited crystals which after recrystallization from ligroin proved to be the more soluble β-II, m.p. and mixture m.p.

α-Phenacylpyridine methobromide (III). The free base liberated from 27.7 g. (0.1 mole) of I hydrobromide was dissolved in 50 ml. of ethanol and treated with 20 ml. of methyl bromide. The reaction took place at room temperature over several days; large rhomboids separated, yield, 21.6 g. (74%). A sample crystallized from ethanol in clusters of colorless plates, m.p. 214.0–214.2° dec.

Anal. Calc'd for $C_{14}H_{14}BrNO$: C, 57.55; H, 4.83; N, 4.79.
Found: C, 57.66; H, 4.89; N, 4.95.

Catalytic reduction of III. A solution of 21.6 g. (0.074 mole) of III in 250 ml. of methanol was shaken with hydrogen at room temperature and atmospheric pressure in the presence of 2 g. of Adams' catalyst. The reduction was stopped after 6.3 l. of gas (3.3 mole-equivalents) had been taken up (twenty-one minutes). After removal of catalyst, the product was freed of solvent and taken up in a small amount of ethanol. A first crop of crystalline IV hydrobromide was obtained on dilution with acetone and two additional crops resulted after evaporation of solvent and treatment with acetone; total yield, 19.4 g. (88%). First and second crop salt (18.1 g., m.p. 145–146°) was dissolved in water and basified with 4 *N* sodium hydroxide; the base was taken up in isopropyl ether and distilled at 1 mm.; yield, 12.3 g. (93% recovery) of somewhat viscous, pale yellow oil, b.p. 124°.

Anal. Calc'd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45.
Found: C, 77.25; H, 8.90; N, 6.42.

The following derivatives of 1-methyl-2-phenacylpiperidine (IV) were examined: the *hydrobromide* emerged slowly from the solution in a small volume of ethanol on dilution (1:1) with acetone, compact clusters of colorless granules which initially appeared cubic, m.p. 148.8–149.4°, analysis for $C_{14}H_{20}BrNO$. The *hydrochloride* crystallized slowly from the conc'd ethanolic solution on addition of about 10 volumes of ether, compact microneedle-clusters, m.p. 172–173° dec. (m.p. 166° on very slow heating), analysis for $C_{14}H_{20}ClNO$. The absorption was measured on an ethanol solution of this salt, $\lambda_{max.}$ 245 mμ ε 14500, $\lambda_{max.}$ 280 mμ ε 1350; in appearance the curve resembles that found for acetophenone (19). The *picrate* formed tiny, bright yellow or orange, granular clusters from ethanol-acetonitrile, m.p. 159.2–159.4°, analysis for $C_{20}H_{22}N_4O_8$. The *acid oxalate* formed puffballs of tiny, white, needle-clusters from isopropyl ether-ethanol, m.p. 131–133°, analysis for $C_{14}H_{19}NO \cdot C_2H_2O_4$. Addition of several drops of 48% hydrobromic acid to a mixture of IV hydrobromide and 2,4-dinitrophenylhydrazine in boiling 95% ethanol brought about solution and then separation of the difficultly soluble *hydrazone hydrobromide* as an orange crystalline solid, m.p. 237–240° dec.; *IV-2,4-dinitrophenylhydrazone* free base formed tiny clusters of orange leaves from isopropyl ether-acetonitrile, m.p. 138.1–138.6°.

The hydrogenation of 21.2 g. (0.0725 mole) of III in 60 ml. of methanol (0.3 g. of catalyst) was carried out as above except that it was allowed to continue until the rate became negligible (seven hours, 8.5 l. of hydrogen = 4.5 mole-equivalents). The regenerated crude free bases (oily) were treated with an equivalent amount of oxalic acid in isopropyl ether-ethanol; in several crops a total of 6.3 g. (28%) of crude IV oxalate (identified by analysis, conversion to hydrochloride and picrate) was obtained. The sirupy bases (12 g.) liberated from the oxalate mother liquors were then treated with 10.8 g. of picric acid in 25 ml. of boiling ethanol and the solution was allowed to cool while acetonitrile was added to maintain clarity. After seeding with IV picrate, the solution slowly deposited a small amount of this salt and, after ten days, a large quantity of bright yellow needle tufts. This crude V *picrate* (yield 6.8 g., 20%) was easily separated from traces of IV picrate since the latter emerges from solution very slowly, even when seeded, while V picrate forms relatively stable supersaturated solutions but comes out rapidly when seeded; it was recrystallized from methanol-acetonitrile, m.p. 131.4–131.8°.

Anal. Calc'd for $C_{14}H_{25}NO \cdot C_6H_3N_3O_7$: C, 53.09; H, 6.24; N, 12.38.
Found: C, 53.13, 53.19; H, 6.11, 6.18; N, 12.36, 12.50.

From the picrate the *free base* V was obtained in 82% yield, b.p. 127–132° at 1.5 mm.; the analytical figures agreed approximately with those calculated for $C_{14}H_{25}NO$. The base absorbed oxygen from the air [autoxidation of a basic ketone, *cf.* (20)]; after several weeks, careful analyses checked closely the empirical composition $C_{14}H_{25}NO_{1.3}$. Attempts to prepare the oxime, 2,4-dinitrophenylhydrazone, phenylurethan, and *p*-nitrobenzoate gave inconclusive results. The *methiodide* crystallized from ethyl acetate-ethanol in clusters of thin, colorless slats, m.p. 163.1–163.5° (sintering from 159°).

Anal. Calc'd for $C_{14}H_{25}NO \cdot CH_3I$: C, 49.32; H, 7.73; N, 3.83.
Found: C, 49.20, 49.28; H, 7.74, 7.80; N, 3.76, 3.86.

Aluminum isopropoxide reduction of IV. A mixture of 10.8 g. (0.05 mole) of freshly-distilled IV, 10 g. of aluminum isopropoxide, and 50 ml. of isopropanol was refluxed while the acetone formed was distilled off. After seven hours, when the distillate gave a negative test for acetone, the remainder of the isopropanol was removed *in vacuo* and the residue was decomposed by aqueous alkali and extracted with benzene. The benzene-soluble product, 10.0 g. of viscous oil, was only partially soluble in acid; the neutral fraction was distilled, yielding 2.6 g. of *phenylmethylcarbinol* (VI) (42%), b.p. 94° at 13 mm., m.p. between 0° and room temperature; *α-naphthylurethan,* colorless needle-clusters from ligroin-isopropyl ether, m.p. 105.6–106.0° [lit. gives for VI: b.p. 94°/12 mm. (21); m.p. 20.1° (22); α-napthylurethan, m.p. 106° (23)]. The basic fraction was liberated, taken up in ether and distilled at 1 mm.: the portion b.p. 74–105° amounted to 1.2 g. (15% calculated as VII); the portion b.p. 127–147° was 2.4 g.; and the residue was *ca.* 2.7 g. The crude VII was an oil and gave an oily picrate; the *methiodide* formed in good yield and crystallized very slowly

from ethyl acetate-ethanol in pale yellow clumps, m.p. 150–165° to cloudy melt, clear at 175° [Hess (13a) prepared two VII-methiodides, m.p. 176° and m.p. 176–177°, mixture m.p. 170–175°].

Anal. Calc'd for $C_{10}H_{22}INO$: C, 40.14; H, 7.41; N, 4.68.
Found: C, 39.79; H, 7.46; N, 4.69.

The fraction b.p. 127–147°/1 mm. was an oil which gave an oily picrate and an oily methiodide; the analysis (C, 76.79; H, 9.91; N, 8.11) indicated the possible presence of 1-methyl-2-(β-hydroxy-β-phenylethyl)piperidine racemates.

SUMMARY

An improved synthesis of α-phenacylpyridine has been described.

The catalytic reduction of α-phenacylpyridine yields the two racemic forms of 2-(β-hydroxy-β-phenylethyl)piperidine. The catalytic reduction of α-phenacylpyridine methobromide gives 1-methyl-2-phenacylpiperidine, in which on further reduction the benzene ring is hydrogenated. The reaction between 1-methyl-2-phenacylpiperidine and aluminum isopropoxide leads to the formation of methylphenylcarbinol and of 1-methyl-2-(β-hydroxypropyl)piperidine.

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