[CONTRIBUTION FROM THE ORGANIC RESEARCH LABORATORIES OF THE U. S. VITAMIN & PHARMACEUTICAL CORP.]

# 2-Phenylimidazolidino[1,2-a]piperidine

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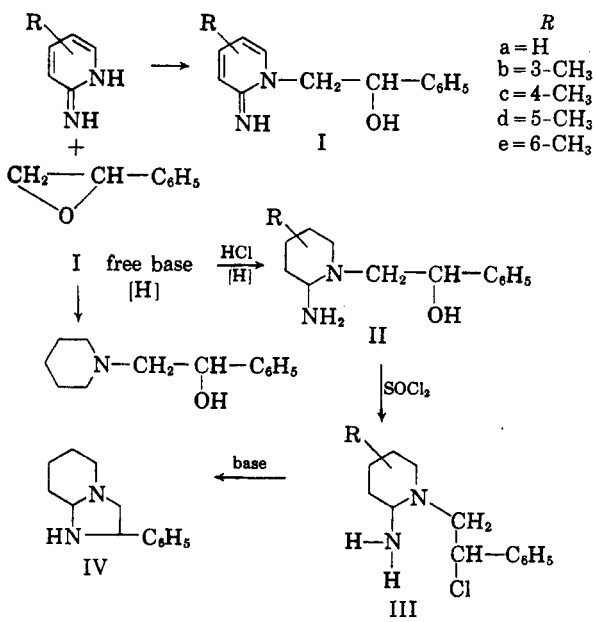
The synthesis of 2-phenylimidazolidino[1,2-*a*]piperidine (IV) has been realized by reaction of styrene oxide with 2-aminopyridines to give 2-(2-imino-1,2-dihydro-1-pyridine)-1-phenylethanols (I) which were reduced as their hydrochlorides with rhodium on carbon to the 2-(2-amino-1-piperidine)-1-phenylethanol hydrochlorides (II). Treatment with thionyl chloride effected conversion to the corresponding chloride (III) which was cyclized to the required IV. Hydrogenation of I as the free base proceeded with loss of ammonia to give 2-(1-piperidine)-1-phenylethanol which was indicative of the structure of I.

For projected synthetic work, 2-phenylimidazolidino[1,2-a]piperidines (IV) were required as reactants[1] for conversions involving replacement of the hydrogen at $N^1$ with functional groups of medicinal chemical interest. The route employed is indicated in Scheme I.

SCHEME I




Other workers have shown, in the absence of alkaline catalyst, that the azine nitrogen of 2-aminopyridine is the predominant nucleophile in reaction with epoxides,[2-4] as it is with halides.[1b,5]

In this work, condensation of 2-aminopyridines with styrene oxide afforded the 2-(2-imino-1,2-dihydro-1-pyridine)-1-phenylethanols (I). This preferred route is of interest in view of evidence demonstrating a ratio of $10^3$:1 for amino to imino form with aminopyridine[6] and would suggest constant formation of the imine tautomer as reaction to I proceeds.

Evidence as the the locus of attack on styrene oxide and structure proof for Ia was obtained by hydrogenation with noted deamination to afford 2-(1-piperidine)-1-phenylethanol, identical with the product obtained from styrene oxide and piperidine[7] (see Scheme I). Such deamination has been observed with aminopyridine,[8] and it was found upon reduction of the hydrochloride of I, that the required 2-(2-amino-1-piperidine)-1-phenylethanol hydrochloride (II) was readily obtained.

The locus of addition of the proton in I in salt formation is unsettled[9] and it is of interest that with aminopyridine, hydrochloric acid forms salts with ring nitrogen, whereas 98% sulfuric acid reacts at the amino nitrogen. The stabilizing effect against deamination during hydrogenation entailed with employment of I as the hydrochloride needs further rationalization.[10]

Conversion to the chloride III was effected by treatment of II with thionyl chloride, and cyclization to the 2-phenylimidazolidino[1,2-a]-piperidine (IV) was achieved by reaction of III in the presence of sodium carbonate or sodium hydroxide as a base. The yields in this last step have been poor (25%).

Of interest, throughout this series is the characterization of the compounds as monopicrates in the

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presence of two accessible nitrogens,[11] which suggests steric factors associated with the proximity of these nitrogens.

Reaction occurred under similar conditions to give the I analog[2] of 4-aminopyridine, whereas 3-aminopyridine failed to react.

Work is in progress with functional derivatives of IV. However, some of these intermediates have pharmacological properties of interest: antiinflammatory (IIa, IVa, Ic),[12] potentiation of adrenaline (Ib, IIb),[13] and ganglionic block (IIb).[13]

## EXPERIMENTAL

*2-(2-Imino-3-methyl-1,2-dihydropyridine)-1-phenylethanol* (Ib). A mixture of 24.0 g. (0.2 mole) of styrene oxide and 32.4 g. (0.3 mole) of 2-amino-3-methylpyridine was stirred at 100° for 6 hr. and 200 ml. of boiling ethanol added. After filtration and upon cooling (3 hr. at 10°), 22.4 g. (49%) of product separated, m.p. 158–161°. Recrystallization (isopropyl alcohol, then acetonitrile) yielded 40% of product, m.p. 166–169°.

*Anal.* Calcd. for $C_{14}H_{16}N_2O$: C, 73.7; H, 7.1. Found: C 73.7; H, 6.7.

The monohydrochloride prepared in ethanol and recrystallized (acetonitrile-propanol) melted at 185–186°.

*Anal.* Calcd. for $C_{14}H_{17}ClN_2O$: C, 63.5; H, 6.5. Found: C, 63.9; H, 6.2.

The monopicrate melted at 136–137° (ethanol).

*Anal.* Calcd. for $C_{20}H_{19}N_5O_8$: C, 52.5; H, 4.2; N, 15.3. Found: C, 52.6; H, 3.9; N, 15.0.

*2-(2-Imino-4-methyl-1,2-dihydro-1-pyridine)-1-phenylethanol* (Ic) was similarly prepared from 2-amino-4-methylpyridine in 13% yield, m.p. 159–160° (ethanol).

*Anal.* Calcd. for $C_{14}H_{16}N_2O$: C, 73.7; H, 7.1; N, 12.3. Found: C, 73.6; H, 7.2; N, 12.4.

The compound was also characterized as its hydrochloride, m.p. 230–231° (ethanol).

*2-(2-Imino-5-methyl-1,2-dihydro-1-pyridine)-1-phenylethanol* (Id) was similarly prepared from 2-amino-5-methylpyridine in 26% yield, b.p. 184–188° (0.4 mm.) and was characterized as its picrate, m.p. 243° dec. (ethanol).

*Anal.* Calcd. for $C_{20}H_{19}N_5O_8$: N, 15.3. Found: N, 15.1.

*2-(2-Imino-6-methyl-1,2-dihydro-1-pyridine)-1-phenylethanol* (Ie) was similarly prepared from 2-amino-6-methylpyridine in 15% yield, b.p. 181–184° (0.3 mm.) and was characterized as its picrate, m.p. 151–153° (ethanol).

*Anal.* Calcd. for $C_{20}H_{19}N_5O_8$: C, 52.5; H, 4.2; N, 15.3. Found: C, 52.4; H, 4.4; N, 15.3.

*2-(2-Imino-1,2-dihydro-1-pyridine)-1-phenylethanol* (Ia). A mixture of 12.0 g. (0.1 mole) of styrene oxide and 14.1 g. (0.15 mole) of 2-aminopyridine was heated at 100° for 6 hr., dissolved in 50 ml. of ethanol and filtered. After cooling (3 hr. at 10°), 7.0 g. (33%) of product was obtained, m.p. 165–166°; recrystallized (ethyl acetate) m.p. 166–169°.[14]

*Anal.* Calcd. for $C_{13}H_{14}N_2O$: C, 72.9; H, 6.6; N, 13.1. Found: C, 73.3; H, 6.8; N, 13.0.

The monohydrochloride was prepared and recrystallized (isopropyl alcohol), m.p. 197–200° dec.

*Anal.* Calcd. for $C_{13}H_{15}ClN_2O$: C, 62.3; H, 6.0; N, 11.2. Found: C, 63.0; H, 6.1; N, 11.9.

*2-(2-Amino-1-piperidine)-1-phenylethanol hydrochloride* (IIa). A solution of 24.9 g. (0.1 mole) of 2-(2-imino-1,2-dihydro-1-pyridine)-1-phenylethanol hydrochloride in 225 ml. of ethanol, after addition of 2.0 g. of 5% rhodium on carbon, was shaken in the Parr hydrogenator at an initial pressure of 4 atm. of hydrogen until the calculated quantity of hydrogen was taken up. After filtration and removal of solvent, 25.0 g. (98%) of product was obtained and recrystallized (methyl ethyl ketone–ethanol), m.p. 184–185°.

*Anal.* Calcd. for $C_{13}H_{21}ClN_2O$: C, 60.8; H, 8.2; N, 10.9. Found: C, 61.1; H, 7.9; N, 10.6.

*2-(Piperidino)-1-phenylethanol.* In the instance of the reduction above, if the free base instead of the hydrochloride is used for reduction, deamination proceeds during the hydrogenation. A mixture of 53.0 g. (0.25 mole) of Ia in 200 ml. of ethanol, and 5.0 g. of 5% rhodium on carbon was treated in the Parr hydrogenator at an initial pressure of 4 atm. of hydrogen. After 7 hr., 0.9 mole of hydrogen had been taken up and no further drop in pressure was observed. Upon removal from the hydrogenator a strong odor of ammonia was noted. After filtration and removal of the solvent, the residue crystallized to give 51.5 g. (100%) of product, m.p. 60–62°; recrystallized (hexane) m.p. 62–64°. A mixed melting point with an authentic sample of 2-piperidine-1-phenylethanol (m.p. 65–67°) showed no depression.

The hydrochloride was recrystallized (acetonitrile), m.p. 126–128°.

*Anal.* Calcd. for $C_{13}H_{20}ClNO$: N, 5.8. Found: N, 5.8.

The picrate melted at 135–137° (ethanol).

*Anal.* Calcd. for $C_{19}H_{22}N_4O_8$: C, 52.5; H, 5.1; N, 12.9. Found: C, 52.9; H, 5.3; N, 13.0.

*2-(2-Amino-3-methyl-1-piperidine)-1-phenylethanol hydrochloride* (IIb). Reduction of 2-(2-imino-3-methyl-1,2-dihydro-1-pyridine)-1-phenylethanol hydrochloride as above afforded the title compound in 29% yield, m.p. 187–188° (acetonitrile).

*Anal.* Calcd. for $C_{14}H_{23}ClN_2O$: C, 62.1; H, 8.6; N, 10.4. Found: C, 61.6; H, 8.8; N, 10.1.

*2-(2-Amino-1-piperidine)-1-phenylethyl chloride hydrochloride* (IIIa). A 25.5-g. (0.1 mole) portion of 2-(2-amino-1-piperidine)-1-phenylethanol hydrochloride was suspended in 250 ml. of anhydrous ether and 14.3 g. (0.12 mole) of thionyl chloride added over 20 min. with stirring. After addition was complete, the ether was decanted from the gummy solid, and the latter, triturated with ether and filtered, gave 25.6 g. of product; recrystallized (acetonitrile), m.p. 182–184°.

*Anal.* Calcd. for $C_{13}H_{20}Cl_2N_2$: C, 56.7; H, 7.3; N, 10.2. Found: C, 56.9; H, 6.6; N, 10.2.

The monopicrate melted at 127–130° (ethanol).

*Anal.* Calcd. for $C_{19}H_{22}ClN_5O_7$: C, 48.8; H, 4.7. Found: C, 48.8; H, 4.3.

*2-(2-Amino-3-methyl-1-piperidine)-1-phenylethyl chloride hydrochloride* (IIIb). In a manner similar to that described above, 2-(2-amino-3-methyl-1-piperidine)-1-phenylethanol hydrochloride was converted by treatment with thionyl chloride to the title compound in 25% yield, m.p. 215–216° (methyl ethyl ketone–ethanol).

*Anal.* Calcd. for $C_{14}H_{22}Cl_2N_2$: N, 9.7. Found: N, 9.5.

The monopicrate melted at 98–99° (ethanol-water).

*Anal.* Calcd. for $C_{20}H_{24}ClN_5O_7$: C, 49.9; H, 5.0; Cl, 25.0. Found: C, 49.6; H, 5.6; Cl, 25.0.

*2-Phenylimidazolidino[1,2-a]piperidine* (IVa). *Method* A: Sodium carbonate (12.7 g., 0.12 mole) was suspended in 150 ml. of refluxing benzene. To this was added dropwise with stirring, a solution of 9.3 g. (0.03 mole) of 2-amino-1-(2-chloro-2-phenyl)ethylpiperidine hydrochloride in 100 ml. of ethanol over 1.5 hr. The reaction mixture was refluxed with stirring for 13 hr., cooled, filtered, and the solvent distilled from the filtrate. The residual oil was extracted with ether, a small amount of solid removed, and after removal of solvent, the residue on distillation gave 11% of product, b.p. 118–120° (0.3 mm.).

*Anal.* Calcd. for $C_{13}H_{18}N_2$: N, 13.9. Found: N, 13.6.

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(11) See refs. 12–14 in S. L. Shapiro, V. A. Parrino, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 4635 (1959).

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(14) Ref. 4 reports m.p. 170–172°.

The monopicrate melted at 176–178° (ethanol).

*Anal.* Calcd. for $C_{19}H_{21}N_5O_7$: N, 16.2. Found: N, 15.9.

*p-Nitrobenzamide* prepared by refluxing with *p*-nitrobenzoyl chloride in benzene was isolated as the *p*-nitrobenzamide hydrochloride, m.p. 188–189° (isopropyl alcohol–isopropyl ether).

*Anal.* Calcd. for $C_{20}H_{22}ClN_3O_3$: C, 61.9; H, 5.7; N, 10.8. Found: C, 61.9; H, 5.6; N, 10.6.

*Method* B: Sodium hydroxide (4.0 g., 0.1 mole) was dissolved in 25 ml. of water and added to 25 ml. of acetonitrile, and a solution of 9.3 g. (0.03 mole) of 2-amino-1-(2-chloro-2-phenyl)ethylpiperidine hydrochloride in 50 ml. of 50% aqueous acetonitrile was admitted over 1 hr. Stirring was continued for a total of 15 hr. after addition was complete. After addition of 50 ml. of water, the acetonitrile was removed and the residue extracted with five 20-ml. portions of ether. After drying and removal of solvent, the residue distilled to give 1.5 g. (25%) of product, b.p. 113–116° (0.2 mm.).

*1-(2-Hydroxy-2-phenylethyl)-4-imino-1,4-dihydropyridine.* A solution of 28.5 g. (0.3 mole) of 4-aminopyridine and 24.0 g. (0.2 mole) of styrene oxide in 110 ml. of ethanol was heated under reflux for 7.5 hr. When cool, the product of 20.0 g. (47%) was separated, m.p. 218–222°; recrystallized m.p. 232–234° (isopropyl ether–methanol). It was not obtained analytically pure.

The picrate melted at 150–152° (ethanol).

*Anal.* Calcd. for $C_{19}H_{17}N_5O_8$: C, 51.5; H, 3.9; N, 15.8. Found: C, 51.4; H, 4.0; N, 15.7.

In a similar reaction with 3-aminopyridine, 62% recovery of the reactant pyridine resulted and some intractable tar.

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# 2-Methyl-2-thiazoline-4-carboxylic Acid: Formation from *N*-Acetylcysteine and Hydrolysis

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Methyl 2-methyl-2-thiazoline-4-carboxylate has been synthesized and hydrolyzed to the corresponding acid. In mineral acid solutions this acid has a characteristic absorption spectrum with a maximum at 261 mμ. In strongly acid solution, *e.g.*, 7*M* hydrochloric acid, the carboxythiazoline is hydrolyzed very slowly, but the velocity of reaction increases with decreasing acid concentration to a maximum at about *p*H 1.7; the products are a mixture of *N*-acetyl- and *S*-acetylcysteine, as well as cysteine and acetic acid. At acid concentrations below 0.2*M* the last products are formed slowly, and a pseudo-equilibrium can be established between thiazoline, *N*-, and *S*-acetylcysteine. *N*-Acetylcysteine in 10*M* sulfuric acid is completely converted to 2-methyl-2-thiazoline-4-carboxylic acid. The amounts and the rates of formation of thiazoline in more dilute solutions of sulfuric or other strong acids have been determined.

The suggestion of Linderstrøm-Lang and Jacobsen[2] that the mercapto groups of proteins may become involved in thiazoline-ring formation has recently been receiving renewed attention, and evidence for the formation of thiazoline derivatives has been obtained in the case of glutathione,[3–6] 2-acetamidoethanethiol,[7] and *N*-formylcysteine.[8] Only in the last case, however, has the thiazoline derivative been isolated.

This paper reports the interconversion of *N*-acetylcysteine and 2-methyl-2-thiazoline-4-carboxylic acid (MTC). The methyl ester of this acid has been synthesized and converted to the acid by hydrolysis; the thiazoline derivatives exhibit a characteristic absorption maximum at 261 mμ by means of which their further reaction can be conveniently studied. The hydrolysis of 2-methyl-2-thiazoline-4-carboxylic acid in various acid concentrations has been investigated. *N*-Acetylcysteine, *S*-acetylcysteine, and the products of complete hydrolysis, acetic acid and cysteine, are formed.

Methyl 2-methyl-2-thiazoline-4-carboxylate hydrochloride was prepared by condensing cysteine methyl ester hydrochloride with ethyl acetimidate hydrochloride, a reaction previously employed to make other thiazoline derivatives.[9] Potentiometric titration of the ester with alkali showed the presence of one group, *p*K 3.05. The spectrum in acid solution, *e.g.*, 1*M* hydrochloric acid, showed a maximum at 261 mμ with a molar absorbancy coefficient of 5500.

Treatment of the ester with 0.1*M* sodium hydroxide for one hour at 40–50° resulted in a product

(1) Cooperative Graduate Fellow, National Science Foundation, 1959–60.

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