[Contribution from the Chemical Laboratory of the University of Illinois]

β-VINYL PIPERIDINE

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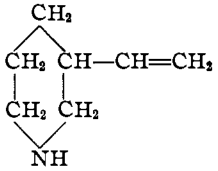
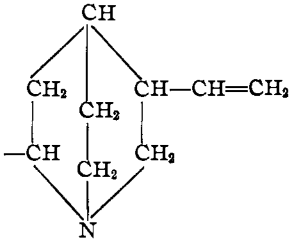
β-Vinyl piperidine (I) is of interest because of its structural relationship to the quinuclidine nucleus (II) of the natural alkaloids of the cinchonine and quinine group.



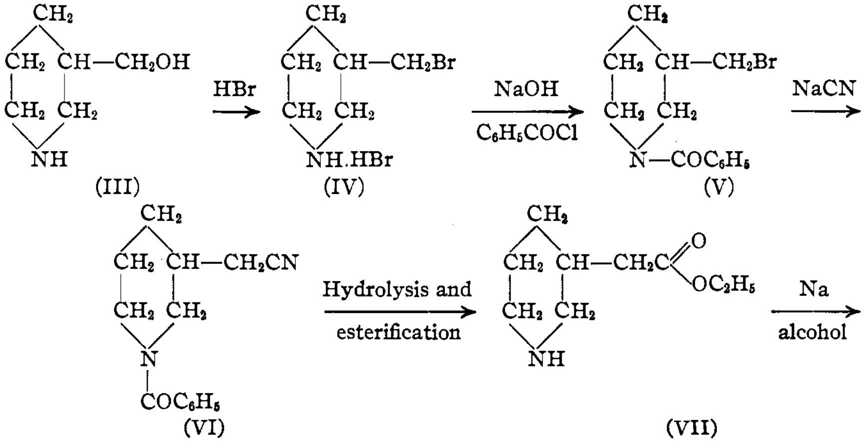
(I)



(II)

The isomeric α-vinyl derivative of piperidine has been prepared and characterized.[2] Lipp and Ladenburg[3] have had some controversy over a compound which is thought to be N-methyl-β-vinyl piperidine. However, the structure of this product has not been proved by a complete synthesis.

β-Vinyl piperidine has been synthesized from β-piperidyl carbinol (III) by the following reactions



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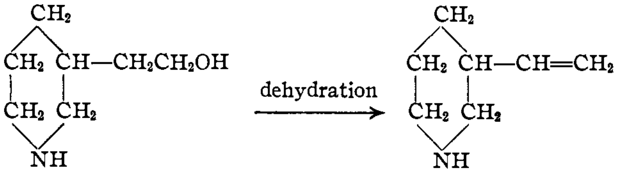
[1] This communication is an abstract of a thesis submitted by Raymond Merchant in partial fulfilment of the requirements for the degree of Doctor of Philosophy, in chemistry, at the University of Illinois.

[2] Ladenburg, *Ber.*, **22**, 2587 (1889).

[3] The references to this work can be obtained from the article by Lipp and Widnmann, *Ann.*, **409**, 79 (1915).



(VIII)

β-Piperidyl carbinol was obtained by the method of Sandborn and Marvel.[4] It was refluxed with constant boiling hydrobromic acid and evaporated to dryness to give a crude β-piperidylmethyl bromide hydrobromide (IV), which in turn was converted to N-benzoyl-β-piperidyl methyl bromide (V). An unsuccessful attempt was made to obtain this compound by preparing N-benzoyl-β-piperidyl carbinol and then reacting with phosphorus tribromide. The bromide would not crystallize and could not be distilled without decomposition. The crude product was used in the preparation of N-benzoyl-β-piperidyl acetonitrile (VI). This compound was also very difficult to obtain pure. It was hydrolyzed by boiling hydrochloric acid and the crude amino acid was esterified with ethyl alcohol. The ethyl-β-piperidyl acetate (VII) thus obtained was isolated in a very pure condition. The reduction of the ester to 2-β-piperidylethanol-1 (VIII) was accomplished with sodium and alcohol.

The dehydration of the primary alcohol was brought about by heating a toluene solution of the amino alcohol with phosphorus pentoxide.[5] The same procedure was used to convert β-piperidyl carbinol to β-methylene piperidine. Only small amounts of these two unsaturated amines were obtained and they could not be purified as carefully as is desirable before the physical properties were determined. However, they were characterized beyond doubt by converting them into solid salts which could be crystallized and thus purified.

Experimental Part

Derivatives of β-Piperidyl Carbinol.—β-Piperidyl carbinol was dissolved in dilute hydrochloric acid and this solution was treated with a slight excess of platinum chloride. The solution was evaporated until crystals appeared and then allowed to stand until crystallization was complete. The crystals were filtered and dried overnight in a desiccator over phosphorus pentoxide; m. p. 174° (uncorr.), decomp.

Anal. Subs., 0.1129; Pt, 0.0338. Calcd. for $(C_6H_{13}ON)_2H_2PtCl_6.H_2O$: Pt, 29.96. Found: Pt, 29.9.

The molecule of water of hydration is lost when the salt stands over phosphorus pentoxide for about two weeks.

Anal. Subs., 0.1496, 0.0985; Pt, 0.0453, 0.0300. Calcd. for $(C_6H_{13}ON)_2H_2PtCl_6$: Pt, 30.49. Found: Pt, 30.28, 30.46.

The chloro-aurate of β-piperidyl carbinol was obtained by mixing a solution of the

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[4] Sandborn with Marvel, This Journal, **50**, 565 (1928).

[5] Compare Löffler and Remmler, *Ber.*, **43**, 2053 (1910).

hydrochloride with a 10% solution of gold chloride, evaporating until crystals appeared and then cooling in an ice-bath. The crystals were separated by filtration and recrystallized from 70% alcohol. The product melted at 153–154° with the evolution of gas.

Anal. Subs., 0.1816; Au, 0.0791. Calcd. for $(C_6H_{13}ON)HAuCl_4$: Au, 43.3. Found: Au, 43.5.

***N*-Benzoyl-β-piperidyl Carbinol.**—To a solution of 9 g. of β-piperidyl carbinol in 100 cc. of water was added, simultaneously during a period of one hour, a solution of 6 g. of potassium hydroxide in 50 cc. of water and 11 g. of benzoyl chloride. Vigorous stirring was maintained during the addition and continued until the odor of benzoyl chloride disappeared. The product was then extracted with benzene and distilled. The product boiled at 213° under 5 mm. On redistillation under very high vacuum (0.01–0.02 mm.) two fractions were obtained. The first fraction (2.7 g.) boiled below 153°; n_D^{25} = 1.5690. On standing it solidified. The second fraction (6 g.) boiled at 153–160°; n_D^{25} = 1.5692. It did not solidify.

The solid compound was recrystallized from an acetone-ether mixture and obtained as a white crystalline product, m. p. 80–81°.

Anal. Subs., 0.1978; CO_2, 0.5178; H_2O, 0.1398. Calcd. for $C_{12}H_{17}NO_2$: C, 71.19; H, 7.83. Found: C, 71.38; H, 7.90.

***N*-Benzoyl-β-piperidyl Acetonitrile.**—Twenty g. of β-piperidyl carbinol was refluxed with 160 g. of 48% hydrobromic acid for about four hours. The solution was evaporated to dryness under reduced pressure, the residue was taken up in another 160g. portion of 48% hydrobromic acid and the solution was refluxed for four hours. The mixture was again evaporated to dryness and the residue was boiled with ethyl acetate and filtered.

The crude solid, which consisted mainly of β-piperidyl-methyl bromide hydrobromide was suspended in 100 cc. of ether and decomposed with a solution of 10 g. of potassium hydroxide in 50 cc. of water. The temperature was held at 0–10° by means of an ice-salt bath. The ether solution of the amine was then treated with 30 g. of benzoyl chloride dissolved in 100 cc. of dry ether and the mixture was stirred and treated with 25 g. of finely powdered potassium hydroxide to remove the hydrogen chloride formed by the reaction.

The ether suspension was treated with ice water to dissolve the excess alkali and salts, the ether layer separated and the aqueous layer extracted once with about 100 cc. of chloroform. The ether and chloroform solutions were mixed and evaporated until the solvents were removed. The residual material was treated with a solution of 6 g. of sodium cyanide in 40 cc. of alcohol and 12 cc. of water and the mixture was refluxed for about 48 hours. The solution was evaporated to dryness and the product extracted from the salt by means of 60 cc. of ethyl acetate. The solvent was evaporated and the residue distilled. The yield of product, b. p. 165–175° (at about 0.1 mm.), was 13–15 g. (33–38% of the theoretical amount). There was 3 g. of lower-boiling material and 4 g. of higher-boiling material which also was mainly the desired product.

The N-benzoyl-β-piperidyl acetonitrile thus obtained is not entirely free from the amide, as is shown by the low values for carbon in the analysis and by the differences between the calculated and observed M_D values.

Anal. (Total carbon.) Subs., 0.4050, 0.3945; CO_2, 648, 627 cc. (*T*, 28°; *P*, 739 mm.). Calcd. for $C_{14}H_{16}N_2O$: C, 73.7. Found: C, 72.7, 72.2. The physical constants on a sample of this purity were: d_4^{20} = 1.1056; n_D^{20} = 1.5602; M_D, calcd., 64.64; found, 66.69.

Ethyl β-Piperidyl Acetate.—Twenty g. of crude N-benzoyl-β-piperidyl acetonitrile was boiled under reflux with 100 cc. of concd. hydrochloric acid for about six hours.

The mixture was cooled and the benzoic acid was removed by extraction with ether. The solution was then evaporated under reduced pressure until all of the water was removed.

The viscous residue was treated with 100 cc. of a 2% solution of dry hydrogen chloride in absolute alcohol and refluxed for about eighteen hours. The solution was evaporated to dryness under reduced pressure. The ester hydrochloride was decomposed by covering with 100 cc. of benzene and then adding slowly 120 g. of a 16% solution of sodium hydroxide. The benzene solution of the free amino ester was separated and the water layer was extracted with another 100 cc. of benzene. The combined benzene extracts were evaporated and the ester was distilled under reduced pressure. The yield of product, b. p. 101–103° (6 mm.), was 4.3 g. (30% of the theoretical amount). The ester is a colorless, limpid liquid; $n_D^{25} = 1.4643$; $d_4^{25} = 1.0131$; M_D, calcd., 46.98; found, 46.62.

Titration. Subs., 0.1150: 9.45 cc. of $N/14$ HCl. Calcd. for $C_9H_{17}NO_2$: neutral equivalent, 171.1; found: 170.

The chloroplatinate was obtained from the hydrochloride and platinum chloride. It melts at 181° and is moderately soluble in water.

Anal. Subs., 0.0727: Pt, 0.0190. Calcd. for $(C_9H_{17}NO_2)_2.H_2PtCl_6$: Pt, 26.1. Found: Pt, 25.95.

2-β-Piperidylethanol-1.—Eleven and one-half g. of ethyl β-piperidyl acetate was dissolved in 200 cc. of boiling absolute alcohol and 10 g. of sodium was added with stirring. The mixture was refluxed for about one-half hour until the sodium was entirely dissolved and then 25 cc. of water was added. The solution was evaporated under pressure and about 30 cc. of water was added in portions from time to time as solid separated. When the volume was about 50–60 cc. the solution was cooled and extracted about five times with 25cc. portions of ether. The ether was evaporated and the residue distilled under reduced pressure. The yield of product, b. p. 121–123° (6 mm.), was 5.5 g. (63% of the theoretical amount). The amino alcohol is a colorless liquid, somewhat less viscous than β-piperidyl carbinol; $n_D^{25} = 1.4888$; $d_4^{25} = 1.0106$; M_D, calcd., 37.73; found: 36.85.

Titration. Subs., 0.0923: 10.10 cc. of $N/14$ HCl. Calcd. for $C_7H_{15}ON$, neutral equivalent, 129.1; found: 127.

Anal. Subs., 0.1700: CO_2, 0.4032 g.; H_2O, 0.1774 g. Calcd. for $C_7H_{15}ON$: C, 65.07; H, 11.71. Found: C, 64.8; H, 11.60.

The chloroplatinate and chloro-aurate were not obtained in the crystalline condition.

β-Methylene Piperidine.—Sixty-five g. of phosphorus pentoxide covered with 25 cc. of toluene was placed in a flask in an oil-bath at 125°. A solution of 10.5 g. of β-piperidyl carbinol in 50 cc. of toluene was added and the solvent was allowed to distil. When most of the toluene was removed, the residue was heated to about 180–190° for two hours. The flask was cooled and the contents were treated with about 200 g. of ice. Solid potassium hydroxide was added until the mixture was strongly alkaline and the mixture was steam distilled until 200 cc. of distillate was obtained. The distillate was first extracted with 100 cc. of ether and the water layer was then acidified with hydrochloric acid and evaporated to dryness.

The ether extract was dried over solid potassium hydroxide. Titration of a sample with standard acid indicated a yield of 20% of the desired amine. The hydrochloride was precipitated by passing dry hydrogen chloride into the ether solution. The precipitate was collected on a filter, washed with ethyl acetate and dried over phosphorus pentoxide.

Anal. Subs., 0.1082, 3.56 cc. of 0.2075 N $AgNO_3$. Calcd. for $C_6H_{12}NCl$: Cl, 27.5. Found: Cl, 27.6.

The hydrochloride obtained from the aqueous and ether portions of two such runs was decomposed with 20 g. of 50% potassium hydroxide solution and the free amine boiled at 125–145°, mainly at 138°. Only 0.4 g. was obtained.

Titration. Subs., 0.1910: 26.7 cc. of $N/14$ HCl. Calcd. for $C_6H_{11}N$, neutral equivalent: 97.1; found, 100. The physical constants on this sample were: n^{20}_{D}, 1.4807; d^{20}_{4}, 0.9342; M_D, calcd., 31.00; found, 29.85.

β-Vinyl Piperidine.—Using a procedure identical with that described above, 12.4 g. of 2-β-piperidylethanol-1 was dehydrated. The hydrochloride came down as a gummy mass. The yield of free base, b. p. 152–155°, was 1.4 g. (13% of the theoretical amount).

Titration. Subs., 0.0824: 6.41 cc. of 0.1138 N HCl. Calcd. for $C_7H_{13}N$: neutral equivalent, 111.1; found, 113.2.

β-Vinyl piperidine of this purity has the following physical constants: $n^{25}_{D} = 1.4731$; $d^{25}_{4} = 0.9274$; M_D, calcd., 35.62; found: 33.61.

The chloroplatinate separated as a gummy solid from water but crystallized from 70% alcohol. The product darkened at 220° and melted with decomposition at 223–224°.

Anal. Subs., 0.1535, 0.0502: Pt, 0.0452, 0.0147. Calcd. for $(C_7H_{13}N)_2.H_2PtCl_6.2H_2O$: Pt, 29.27. Found: Pt, 29.5.

Summary

β-Vinyl piperidine has been prepared from β-piperidyl carbinol and most of the intermediate products have been isolated and characterized.

URBANA, ILLINOIS

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE STATE UNIVERSITY OF IOWA]

FURTHER OBSERVATIONS CONCERNING THE MIGRATION OF ACYL FROM NITROGEN TO OXYGEN

BY L. CHAS. RAIFORD AND F. C. MORTENSEN

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Studies published from this Laboratory[1] have shown that, in general, but one acetyl-benzoyl derivative of an ortho-aminophenol can be obtained, regardless of the order in which the radicals are introduced.[2] When one of the reacting groups (amino and hydroxyl) is on a side chain, as in *o*-hydroxybenzylamine and its isomeride, *o*-aminobenzyl alcohol, isomeric mixed diacyl derivatives were obtained and no rearrangement was observed.[3] This behavior, as well as the results reported by Auwers and co-workers[4] to the effect that they observed a rearrangement in which acyl wandered from oxygen to nitrogen when oxygen was attached to the ring and nitrogen was on a side chain, raised the question of the extent to which this migration is influenced by the cyclic radical of the starting

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[1] Raiford and Lankelma, THIS JOURNAL, **47**, 1111 (1925).

[2] For exceptions, see Raiford and Couture, *ibid.*, **46**, 2307 (1924).

[3] Raiford and Clark, *ibid.*, **45**, 1738 (1923).

[4] Auwers and others, *Ber.*, **33**, 1923 (1900).