three-quarter hours at a rate such that the temperature of the solution was maintained at 20–25°. At the time of the first addition of zinc about 0.1 g. of cupric acetate was added. After addition of the last portion of zinc, 80 ml. of concentrated hydrochloric acid was added and the temperature was then maintained at 32–35° while stirring for the next two and one-half hours. While cooling, enough sodium hydroxide was added to redissolve the initially precipitated zinc hydroxide. A small amount of water was added to dissolve precipitated sodium chloride. The alkaline solution was thrice extracted with chloroform. The chloroform extracts were combined and dried overnight with anhydrous sodium carbonate. After filtering off the carbonate and distilling off the chloroform, the oil residue was distilled to yield 17.0 g. of colorless distillate (b. p. 122–130° at 15 mm.).

Addition of a portion of the distillate to excess aqueous picric acid gave a picrate melting at 158–160° after crystallization from methanol or water. The melting point of a mixture with N-methylmyosmine picrate (IV picrate) was 140–145°. The melting point of a mixture with dihydrometanicotine picrate[10] was 145–152°. The remainder of the base was purified through the picrate and then reconverted to the base (b. p. 124° at 20 mm.). Addition of a small amount of the dihydronicotyrine to excess alcoholic styphnic acid solution gave yellow crystals of a styphnate which melted with decomposition at 198–200°. Treatment of 0.2 g. of the dihydronicotyrine with 0.2 g. of 2,4-dinitrophenylhydrazine in hot alcohol solution containing a little concentrated hydrochloric acid produced no derivative. Upon concentrating and cooling only 2,4-dinitrophenylhydrazine precipitated.

Alkali Treatment of Dihydronicotyrine.—When 0.1 g. of dihydronicotyrine was dissolved in 20 ml. of dilute aqueous sodium hydroxide solution and allowed to stand for one month the picrate obtained from it at the end of that time was still that of unchanged dihydronicotyrine.

A solution of 0.2 g. of dihydronicotyrine in 20 ml. of ethylene glycol containing one pellet of sodium hydroxide was refluxed for seven hours. After diluting with 8 ml. of water the solution was acidified by addition of a few drops of concentrated hydrochloric acid. A picrate was formed by adding excess aqueous picric acid. After crystallizing from water the picrate melted at 215–218°. The melting point of a mixture with nicotine picrate was 218–220°. Concentration of the filtrate from the picrate crystallization gave only a gummy picrate.

Acid Treatment of Dihydronicotyrine.—A solution of 0.1 g. of dihydronicotyrine in 20 ml. of concentrated hydrobromic acid was refluxed for twelve hours. After evaporating on the steam-bath to a viscous sirup it was added to excess aqueous picric acid solution. The picrate, after repeated crystallization from water and from alcohol, had a melting range of 150–175°. The melting point of a mixture with dihydronicotyrine picrate was 155–165°. Mixture with nicotyrine picrate gave a melting point of 142–150°. The melting point of a mixture with N-methylmyosmine picrate (IV picrate) was 140–150°.

Acknowledgment.—The authors are indebted to Ruth Brand and Jane Dixon for the elemental analyses, to Leopold Weil of this laboratory for the ultraviolet absorption spectrum and to the Cliffs–Dow Chemical Company, Marquette, Michigan for a generous sample of pyrrolidone-2.

Summary

Pseudo-oxynicotine dihydrochloride was identified as 3-pyridyl 3-methylaminopropyl ketone dihydrochloride which upon alkalization and distillation yielded 1-methyl-2-(3-pyridyl)-2-pyrroline (N-methylmyosmine).

Contrary to a previous report the zinc-acid reduction of 3,2′-nicotyrine did not produce N-methylmyosmine but produced a dihydronicotyrine of uncertain structure.

N-Methylmyosmine underwent ready polymerization upon standing while dihydronicotyrine did not.

Though acid and alkali did have some effect upon dihydronicotyrine at elevated temperatures no clear-cut evidence of isomerism of dihydronicotyrine into N-methylmyosmine was found.

PHILADELPHIA 18, PA. RECEIVED AUGUST 12, 1949

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[10] Wibaut and Gitsels, *Rec. trav. chim.*, **52**, 303 (1933).

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT OF THE AMERICAN TOBACCO COMPANY]

Rearrangement of Nicotine Oxide

BY C. H. RAYBURN, W. R. HARLAN AND H. R. HANMER

Two isomers of nicotine oxide were described by Pinner and Wolffenstein[1] and Pinner,[2] who named them pseudo-oxynicotine and nicotone. Pseudo-oxynicotine has been identified as 3-pyridyl 3-methylaminopropyl ketone by Haines and Eisner.[3]

Nicotine oxide (I) was pyrolyzed to an isomeric, volatile base by heating *in vacuo* to 200°. The dipicrate melted at 184° when first prepared, agreeing with the melting point of nicotone dipicrate,[2] though further purification raised the melting point to 194–195°. The similarity in method of preparation and properties of the compounds indicates that the base is identical with Pinner's nicotone.

That this base is 2-methyl-6-(3-pyridyl)-tetrahydro-1,2-oxazine (II) is shown by its conversion to 3-pyridyl 3-methylaminopropyl ketone (III) by heating with hydrochloric acid, and by its reduction to 4-methylamino-1-(3-pyridyl)-1-butanol (IV). The structure of IV was proven by dehydration to a mixture of nicotine (V) and metanicotine (VI).

The melting points of the dipicrate and the mercuric chloride derivatives differentiate II from its isomer, 3-pyridyl 3-methylaminopropyl ketone.[3] Tests for aldehyde and ketone groups with II gave negative results. The ultraviolet absorption spectrum in 0.1 *N* hydrochloric acid (Fig. 1) showed only one maximum, at 257.5 mμ, ($\epsilon_M = 5,600$) and was almost identical with that of nicotine oxide ($\epsilon_M = 5,677$ at 257.5 mμ). The

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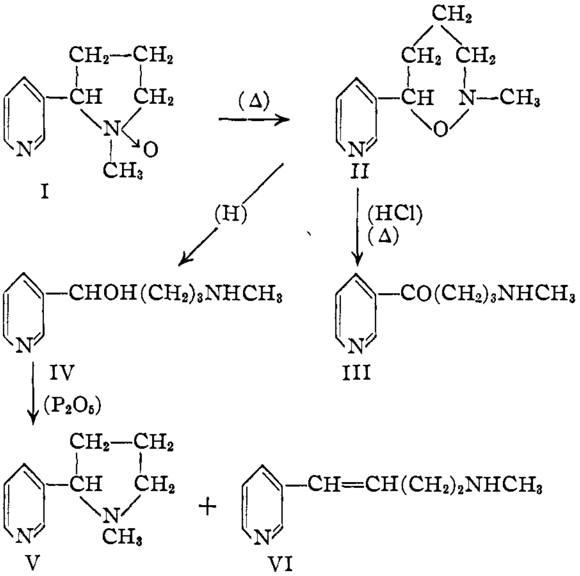
[1] Pinner and Wolffenstein, *Ber.*, **25**, 1428 (1892).

[2] Pinner, *ibid.*, **28**, 456 (1895).

[3] Haines and Eisner, THIS JOURNAL, **72**, 1719 (1950).



similarity of the titration curves of II and nicotine oxide indicates that the oxygen is still attached to the nitrogen atom.

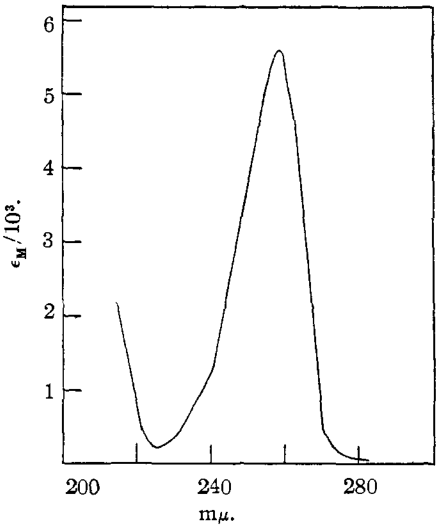


Fig. 1.—Ultraviolet absorption spectrum of 2-methyl-6-(3-pyridyl)-tetrahydro-1,2-oxazine dihydrochloride in 0.1 N hydrochloric acid.

Meisenheimer[4] observed a similar rearrangement of methylallylaniline-N-oxide to N-methyl-O-allyl-phenylhydroxylamine. Both rearrangements involve the transformation of a non-volatile amine oxide to a volatile hydroxylamine derivative.

Experimental

2-Methyl-6-(3-pyridyl)-tetrahydro-1,2-oxazine (II).—Forty-one grams of nicotine oxide (I) was heated in a distilling flask at 1 mm. pressure. At a temperature of 190–200° (oil-bath) a liquid began to distil and continued until only a small amount of tar remained in the flask. The yield of distillate was 39.9 g. (97.3%). Aqueous picric acid added to an aqueous solution of the base gave a dipicrate, m. p. 184°. II was purified by dissolving in ethanol and saturating with hydrogen chloride while cooling. The dihydrochloride was recrystallized from a small volume of water. The yield was 33 g. (57.1% from I), m. p. 187–188°. Aqueous picric acid added to an aqueous solution of the dihydrochloride gave a dipicrate which after recrystallization from water melted at 194–195°. Further crystallizations from water and ethanol did not raise the melting point.

Anal. Calcd. for $C_{22}H_{20}N_8O_{15}$: C, 41.51; H, 3.17. Found: C, 41.88; H, 3.14.

The mercuric chloride derivative was prepared by adding an aqueous solution of II dihydrochloride to a saturated solution of mercuric chloride. After two crystallizations from water a constant melting point, 155–156°, was obtained.

The base was recovered from the dihydrochloride by adding aqueous 20% sodium hydroxide, extracting with chloroform, evaporating the chloroform and distilling at 90° (1 mm.). A colorless liquid was obtained, n^{25}_D 1.5252.

Anal. Calcd. for $C_{10}H_{14}N_2O$: C, 67.39; H, 7.92. Found: C, 67.35; H, 7.69.

After several hours exposure to air the liquid became yellow. Overnight the color changed to blue, and after several days the liquid became dark brown.

No evidence of any reaction was observed on heating II with 2,4-dinitrophenylhydrazine, phenylhydrazine, semicarbazine or hydroxylamine. Ammoniacal silver nitrate was not reduced.

On distillation at atmospheric pressure considerable decomposition took place. Distillation began at about 240° and continued to 255°, leaving a large amount of tar in the distilling flask. Nicotine and unchanged II were identified in the distillate by formation of the dipicrates. Pinner[2] reported that nicotone distilled unchanged at 253°.

Electrometric titration of I and II with 0.1 N hydrochloric acid gave identical curves, beginning at pH 6.85 and showing no break until two equivalents of hydrochloric acid had been added. Dipicrates prepared from the solutions after titration showed that neither base had been converted to the other.

3-Pyridyl 3-Methylaminopropyl Ketone (III).—Ten grams of the dihydrochloride of II and 5 ml. concd. hydrochloric acid were heated four hours at 140°. The mixture was cooled, added to excess magnesium oxide and distilled with superheated steam. The distillate was acidified with hydrochloric acid and evaporated to dryness. The residue, dissolved in absolute alcohol and treated with an equal volume of pentane while cooling, gave a yield of 0.95 g. of the dihydrochloride of III, m. p. 197–198°. The melting points of the dipicrate (128–130° after crystallization from water) and of the mercuric chloride derivatives (211–213°) agreed with those reported by Haines and Eisner.[3]

4-Methylamino-1-(3-pyridyl)-1-butanol (IV).—Forty-two grams of the dihydrochloride of II was dissolved in 200 ml. of 10% acetic acid and 42 g. of zinc dust was added in small amounts while stirring. After four hours the solution was filtered, aqueous 20% sodium hydroxide was added until the precipitate of zinc hydroxide redissolved, and the solution was extracted with chloroform. The chloroform was evaporated and the residue was distilled *in vacuo*. A yield of 25.5 g. (84.5%) of a light yellow, viscous oil was obtained; b. p. 139–140° (1 mm.). The dipicrate precipitated as an oil on adding aqueous picric acid to an aqueous solution of IV. It crystallized slowly, and when dissolved in hot water or alcohol it again separated as an oil on cooling and then crystallized; m. p. 137–138°.

Anal. Calcd. for $C_{22}H_{22}N_8O_{15}$: C, 41.38; H, 3.47. Found: C, 41.40; H, 3.49.

Von Braun and Weissbach[5] reported the melting point

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[4] Meisenheimer, *Ber.*, **52B**, 1667 (1919).

[5] Von Braun and Weissbach, *ibid.*, **63B**, 2018 (1930).

to be 127–128° for the dipicrate of IV obtained by heating nicotine with hydrocinnamic acid.

Dehydration of 4-Methylamino-1-(3-pyridyl)-1-butanol (IV) to Nicotine (V) and Metanicotine (VI).—Five grams of IV and 30 g. of phosphorus pentoxide were refluxed in 100 ml. of xylene for two hours. The mixture was cooled and decomposed with ice. The water layer was separated, made alkaline with 20% sodium hydroxide and distilled with steam. A precipitate formed immediately on adding aqueous picric acid to the distillate. This was filtered off and recrystallized from water. The melting point was 219–220°, and a mixture with nicotine dipicrate showed no depression of the melting point.

The filtrate from the nicotine dipicrate deposited a precipitate on cooling and standing for several days. After recrystallization from water it melted at 163–164°, and no depression of the melting point was observed on mixing with metanicotine dipicrate.

Summary

Nicotine oxide rearranges to form 2-methyl-6-(3-pyridyl)-tetrahydro-1,2-oxazine when pyrolyzed *in vacuo*.

RICHMOND 24, VIRGINIA RECEIVED JULY 27, 1949

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF INDIANA UNIVERSITY]

Substituted Bromoquinolines[1]

BY C. E. KASLOW AND WILLIAM R. LAWTON[2]

In a study of orientation in certain substitution reactions of phenylquinolines, it was found convenient to use bromine substituted phenylquinolines as reference compounds. This paper is a report on the synthesis of some of these derivatives.

It was found that the use of phosphorus pentabromide to replace the hydroxy group by a bromine atom also caused substitution in other positions. Presumably, one of the bromine atoms entered position 3. The structures of these polybrominated phenylquinolines have not yet been proved.

In this work, 2-(4′-bromophenyl)-4-hydroxyquinoline was prepared by the condensation of ethyl anthranilate and *p*-bromoacetophenone diethyl acetal in diphenyl ether at an elevated temperature. 2-Phenyl-4-hydroxyquinoline was prepared from ethyl benzoylacetate and aniline by a modification of the general Conrad–Limpach procedure, using boiling diphenyl ether as the medium for ring closure. The use of *p*-bromoaniline instead of aniline gave 6-bromo-2-phenyl-4-hydroxyquinoline by the same procedure. The action of phosphoryl tribromide on the above 4-hydroxyquinolines gave the corresponding 4-bromoquinolines.

Experimental

***p*-Bromoacetophenone Diethyl Acetal** (I).—This substance was prepared according to the method of Pfeiffer and Adkins.[3] A solution of 20 g. (0.1 mole) of *p*-bromoacetophenone and 24 g. (0.16 mole) of ethyl orthoformate in 65 ml. of absolute ethanol, containing about 0.1 g. of dry hydrogen chloride, was allowed to stand at room temperature for twenty-four hours. After adding a sodium ethoxide solution to neutralize the hydrogen chloride, the main portion of the solvent was removed by distillation and the residue was distilled in vacuum. The main fraction was redistilled, giving 18.2 g. (65%) of colorless I; b. p. 153–155° at 24 mm.

Anal. Calcd. for $C_{12}H_{17}BrO_2$: Br, 29.28. Found: Br, 29.22.

2-(4′-Bromophenyl)-4-hydroxyquinoline (II).—This substance was prepared from I and ethyl anthranilate essentially according to the method of Fuson and Burness.[4] After assembling the apparatus, a mixture of 10 g. (0.06 mole) of ethyl anthranilate, 15 g. (0.06 mole) of I and 100 ml. of phenyl ether was heated in the reaction flask at 120° for thirty minutes, then at 200° for an additional thirty minutes while oxygen-free nitrogen gas was bubbled through the reaction mixture. The nitrogen gas was shut off and the phenyl ether solution refluxed gently for ten hours. After the reaction mixture cooled, the solid was removed by filtration and washed twice with small portions of ligroin and finally with ether. The crude substance (m. p. 318–320°) was recrystallized from butyl cellosolve yielding 5.5 g. (34%) of fine tan-colored needles, m. p. 320–321°.

Anal. Calcd. for $C_{15}H_{10}BrNO$: Br, 26.62. Found: Br, 26.59.

2-(4′-Bromophenyl)-4-bromoquinoline (III).—One gram of II was heated with 2 g. of phosphoryl tribromide[5] in a bath heated to 135–140°. After cooling, the reaction mixture was warmed with 50 ml. of water, then cooled, the solution made alkaline, the solid removed by filtration, dried and extracted with 50 ml. of ligroin. After concentration to 15–20 ml., the substance gave white, silky needles, m. p. 119–120°. Recrystallization of the substance from alcohol gave 1.1 g. (91%) of III, m. p. 120–120.5°.

Anal. Calcd. for $C_{15}H_9Br_2N$: Br, 44.02. Found: Br, 43.89.

2-Phenyl-4-hydroxyquinoline (IV).—A 1-l. flask was fitted with a water-trap for use with an immiscible liquid heavier than water and a reflux condenser was attached to the trap. A mixture of 300 ml. of chloroform, 100 g. (1.1 moles) of aniline, 110 g. (1 mole) of ethyl benzoylacetate and 2–3 drops of 10% sulfuric acid was refluxed gently in the apparatus until no more water was collected in the trap (twenty hours). After removal of the chloroform, first by distillation and finally at reduced pressure, the residue was dissolved in 300 ml. of hot phenyl ether and added slowly to 500 ml. of boiling phenyl ether in a 3-l. flask to which was attached a water-cooled condenser by means of a wide exit tube having about a 20-cm. vertical section. The rate of heating was maintained so that the phenyl ether refluxed in the tube but did not pass into the condenser with the alcohol vapor. When no more alcohol

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[1] Constructed from a Senior Thesis submitted in February, 1947, by William R. Lawton.

[2] Present address: Devoe Reynolds Paint and Varnish Company, Louisville, Kentucky.

[3] Pfeiffer and Adkins, THIS JOURNAL, **53**, 1048 (1931).

[4] Fuson and Burness, *ibid.*, **68**, 1270 (1946).

[5] Fernelius, "Inorganic Syntheses," Vol. II, McGraw-Hill Book Co., Inc., New York, N. Y., 1946, p. 151; see also Gerrard, Nechvatol and Wyvill, *Chemistry and Industry*, 437 (1947).