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*.

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[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

(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).

distilled, the reaction mixture was cooled, filtered and the solid washed with a 150-ml. portion each of ligroin and ether. After two recrystallizations of the crude IV from ethyl alcohol, a yield of 122 g. (55%) of light tan-colored crystals was obtained, m. p. 252–254°. The melting recorded by Conrad and Limpach[6] was 254°.

2-Phenyl-4-bromoquinoline (V).—This substance was prepared from 10 g. of IV according to the method used for the preparation of III; recrystallized from 70% ethyl alcohol, the yield was 10.8 g. (83.5%), m. p. 90–90.5°. The melting point reported by John[7] was 91°.

Using phosphorus tribromide, the yield of V was only 39%. When phosphorus pentabromide was used, the yield of V was 65% but a 7% yield of a by-product (VI) was obtained the analysis of which indicated it was a tribromophenylquinoline, m. p. 149.5–150°.

Anal. Calcd. for $C_{15}H_8Br_3N$: Br, 54.25. Found: Br, 54.32.

2-Phenyl-3-bromo-4-hydroxyquinoline (VIII).—This substance was prepared according to a method reported by Riegel.[8] A solution of 53 g. (0.25 mole) of IV in 300 ml. of hot glacial acetic acid, contained in a 500-ml. three-necked flask fitted with a stirrer, thermometer and a separatory funnel, was treated at 70° over a period of forty-five minutes with 46 g. (0.28 mole) of bromine. After the reaction mixture cooled, a dilute aqueous solution containing 40 g. of sodium hydroxide was added, the crude VII removed by filtration, washed thoroughly with water and dried in an air-bath. The substance was recrystallized three times from methyl alcohol, yielding 68 g. (94%) of fine white needles, m. p. 263–264°.

Anal. Calcd. for $C_{15}H_{10}BrNO$: Br, 26.62. Found: Br, 26.49.

2-Phenyl-6-bromo-4-hydroxyquinoline (VIII).—This substance was obtained from 24 g. of *p*-bromoaniline and 24 g. of ethyl benzoylacetate according to the method for the preparation of IV. After recrystallization of the crude VIII from butyl cellosolve, it was obtained in a 58% yield (24.5 g.) as a fine, white crystalline product, m. p. 331–333°.

Anal. Calcd. for $C_{15}H_{10}BrON$: Br, 26.62. Found: Br, 26.54.

2-Phenyl-4,6-dibromoquinoline (IX).—This substance was prepared from VIII by the action of phosphoryl tribromide, as described for 2-phenyl-4-bromoquinoline. After two recrystallizations from ligroin, the substance was obtained as silky white crystals in a 70% yield, m. p. 121.5–122°.

Anal. Calcd. for $C_{15}H_9Br_2N$: Br, 44.02. Found: Br, 44.10.

2-Phenyl-6-bromo-4-chloroquinoline.—This substance was obtained in 84% yield from 5 g. of VIII by the action of 20 g. of hot phosphoryl trichloride and recrystallization of the crude substance from ethyl alcohol; m. p. 113.5–114°.

Anal. Calcd. for $C_{15}H_9BrClN$: BrCl, 36.21. Found: BrCl, 36.13.

Action with Phosphorus Pentabromide.—Five grams (0.017 mole) of VIII was heated at 105–110° with 15 g. (0.037 mole) of phosphorus pentabromide for three hours, then the reaction mixture was cooled, warmed with water and finally made alkaline with sodium hydroxide. After drying the solid, it was extracted with ligroin (b. p. 60–90°), the solvent concentrated to a small volume and the solid recrystallized three times from ligroin. The yield of the fine white solid was 4.2 g., m. p. 178–179°.

Anal. Calcd. for $C_{15}H_7Br_4N$: Br, 61.37. Found: Br, 61.23.

When 2.5 g. of VII was treated with 5 g. of phosphorus pentabromide as in the case of VIII, there was obtained after extraction with ligroin and recrystallization from methanol, 2.2 g. of a white solid which melted at 166–167°.

Anal. Calcd. for $C_{15}H_7Br_4N$: Br, 61.37. Found: Br, 61.08.

(6) Conrad and Limpach, *Ber.*, **21**, 521 (1888).

(7) John, *J. prakt. Chem.*, **126**, 220 (1930).

(8) Riegel, Lappin, Albisetti, Adelson, Dodson, Ginger and Baker, THIS JOURNAL, **68**, 1229 (1946).

Summary

Several new bromo-2-phenylquinolines have been reported; these are, namely, 2-(4′-bromophenyl)-4-hydroxyquinoline, 2-(4′-bromophenyl)-4-bromoquinoline, 2-phenyl-3-bromo-4-hydroxyquinoline, 2-phenyl-6-bromo-4-hydroxyquinoline, 2-phenyl-4,6-dibromoquinoline and 2-phenyl-6-bromo-4-chloroquinoline.

It has been shown that polybromination may occur when phosphorus pentabromide is used to convert the 2-phenyl-4-hydroxyquinolines to 2-phenyl-4-bromoquinolines.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

A Synthesis of Streptidine[1]

BY M. L. WOLFROM, S. M. OLIN[2] AND W. J. POLGLASE[2]

That component of streptomycin designated streptidine[3] was degradatively established[4] as 1,3-diguanidino-2,4,5,6-tetrahydroxycyclohexane by Carter,[5,6] Folkers,[3,7–9] Wintersteiner,[10,11] and

(1) The synthesis of streptamine from D-glucosamine was reported by M. L. Wolfrom and S. M. Olin before the Division of Sugar Chemistry and Technology and recorded in Abstracts of Papers, 113th Meeting, American Chemical Society, Chicago, Illinois, April, 1948, p. 5Q. A preliminary report by M. L. Wolfrom and W. J. Polglase, of the synthesis of streptidine from streptamine appeared in THIS JOURNAL, **70**, 1672 (1948).

(2) Bristol Laboratories Research Fellow of The Ohio State University Research Foundation (Project 224).

(3) N. G. Brink, F. A. Kuehl, Jr., and K. Folkers, *Science*, **102**, 506 (1945).

(4) R. U. Lemieux and M. L. Wolfrom, *Advances in Carbohydrate Chem.*, **3**, 337 (1948), review paper.

(5) H. E. Carter, R. K. Clark, Jr., S. R. Dickman, Y. H. Loo, P. S. Skell and W. A. Strong, *J. Biol. Chem.*, **160**, 337 (1945); *Science*, **103**, 540 (1946).

(6) H. E. Carter, R. K. Clark, Jr., S. R. Dickman, Y. H. Loo, J. S. Meek, P. S. Skell, W. A. Strong, J. T. Alberi, Q. R. Bartz, S. B. Binkley, H. M. Crooks, Jr., I. R. Hooper and Mildred C. Rebstock, *ibid.*, **103**, 53 (1946).

(7) R. L. Peck, R. P. Graber, A. Walti, Elizabeth W. Peel, C. E. Hoffhine, Jr., and K. Folkers, THIS JOURNAL, **68**, 29 (1946).

(8) R. L. Peck, C. E. Hoffhine, Jr., Elizabeth W. Peel, R. P. Graber, F. W. Holly, R. Mozingo and K. Folkers, *ibid.*, **68**, 776 (1946).

(9) F. A. Kuehl, Jr., R. L. Peck, C. E. Hoffhine, Jr., R. P. Graber and K. Folkers, *ibid.*, **68**, 1460 (1946).

(10) J. Fried, G. A. Boyack and O. Wintersteiner, *J. Biol. Chem.*, **162**, 391 (1946).

(11) J. Fried and O. Wintersteiner, THIS JOURNAL, **69**, 79 (1947).