with 20% sodium hydroxide and mechanically agitated for thirty minutes, washed with 10% sodium thiosulfate solution, filtered and distilled to remove unreacted thiophene. The product boiled at 113–117° (1.5 mm.); yield 169 g. (90%). The distillate had a green cast that was removed by three recrystallizations from a mixture of equal parts of petroleum ether and absolute ether; m. p. 56–57°; the mixed melting point with an authentic sample[8] was 56–57°.

The oxime melted at 92.5–93°.[9]

2-Acetylfuran.—To an agitated mixture of 58 g. (0.85 mole) of furan and 107 g. (1 mole) of 95% acetic anhydride cooled to 0° was added 2.5 g. of 56% hydriodic acid. The reaction proceeded very rapidly and the mixture was maintained at 0–25° by means of the Dry Ice–acetone bath. After the reaction ceased, the mixture was allowed to warm to room temperature and stirred thirty minutes longer. After the addition of 200 ml. of water, the mixture was stirred for fifteen minutes. The organic layer was drawn off and the aqueous layer washed twice with 50-ml. portions of chloroform. The organic layers were combined and washed with 10% sodium carbonate solution until neutral and finally washed thoroughly with a 10% solution of sodium thiosulfate. The organic layer was dried over anhydrous sodium sulfate and then filtered into a Vigreux-modified Claisen flask, the chloroform removed at atmospheric pressure. The product boiled at 45–48° (5 mm.), m. p. 30–32°.[10] Three grams of crystalline residue was not identified but may have been 2,5-diacetylfuran. The 2,4-dinitrophenylhydrazone melted at 219–220°.[11]

(8) Stadnikoff and Goldfarb, *Ber.*, **61B**, 2341 (1928).

(9) Stadnikoff and Rakovski (*ibid.*, **61B**, 268 (1928)) reported 93°.

(10) Reichstein (ref. 4) reported 30–32°.

Acknowledgment.—The authors are very grateful to Dr. Darwin E. Badertscher for his advice and interest in this problem. The authors wish to thank Miss Josephine Sidoni and Mr. John J. Sardella for their coöperation in carrying out some of the laboratory preparations.

Summary

1. Catalytic quantities of iodine and hydriodic acid have been shown to promote the acylation of furan and thiophene.

2. Yields of 2-acetylthiophene as high as 86% are reported when 8×10^{-3} mole of iodine per mole of acetic anhydride is employed with thiophene and acetic anhydride. 2-Benzoylthiophene has been obtained in yields of the order of 90% from benzoyl chloride and thiophene.

3. 2-Acetylfuran has been prepared from furan and acetic anhydride in yields of 60 and 76% when iodine and hydriodic acid, respectively, are used as catalysts.

(11) Chute, Orchard and Wright [*J. Org. Chem.*, **6**, 165 (1941)] found 223°.

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[CONTRIBUTION FROM THE NOYES LABORATORY OF CHEMISTRY, UNIVERSITY OF ILLINOIS]

The Preparation of Unsymmetrical Diaryl Amines. 5-Phenylamino-6-methoxy-8-(3-diethylaminopropylamino)-quinoline[1]

BY H. R. SNYDER AND NELSON R. EASTON

There are several known examples of the reaction of aromatic nitroso compound with a phenol or an aromatic amine to form the anil of a quinone. For example, Euler[2] reported that nitrosobenzene reacts with α- or β-naphthol to give the phenylanil of the corresponding naphthoquinone, and Kaufler and Suchannek[3] have described a similar reaction between *p*-nitrosodimethylaniline and 9-anthrol or 9-anthramine. Thus it would appear that certain phenols and primary aromatic amines might be converted to their *o*- or *p*-arylamino derivatives by condensation with the appropriate nitroso compound and reduction of the resulting anil. This possibility was particularly attractive in connection with the application to the synthesis of 5-phenylamino-6-methoxy-8-aminoquinoline (II) from 6-methoxy-8-aminoquinoline; the diethylaminopropyl derivative (III) of the base II was desired for testing as an antimalarial agent.

The anil (I) was obtained in about 60% yield when the reaction was carried out in aqueous *i*-propyl alcohol under mild conditions. When the reaction was attempted in glacial acetic acid solution none of the product (I) was obtained; the dark-colored, tarry material that formed in this experiment may have contained some of the isomeric azo compound (6-methoxy-8-benzeneazoquinoline). The reduction of the anil to the diaminoquinoline (II) could be effected with phenylhydrazine, stannous chloride and hydrochloric acid, or hydrogen and platinum oxide catalyst. The desired drug (III) was obtained by the treatment of II with 3-diethylaminopropyl chloride.

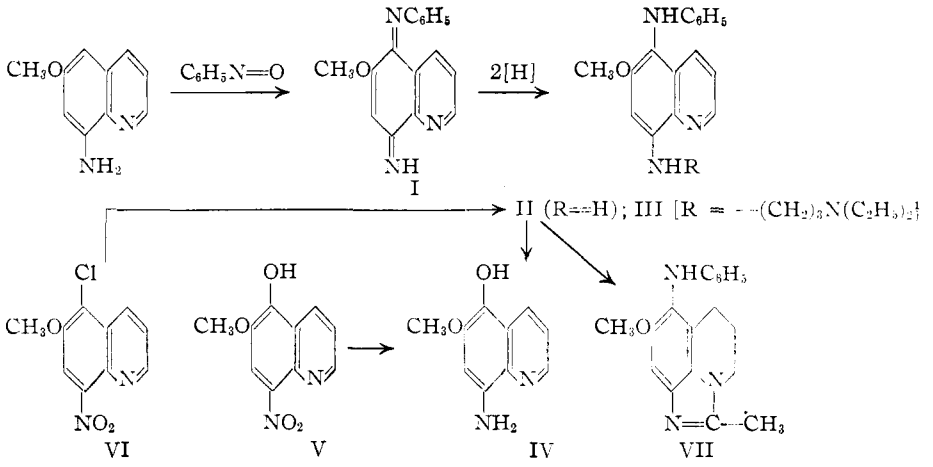
Because of the possibility that the initial condensation might have produced 6-methoxy-8-benzeneazoquinoline rather than the anil (I), rigorous proof of the structure of the product was sought. The reduction product (II) underwent cleavage of the phenylamino group on treatment with hot dilute hydrochloric acid, yielding 5-hydroxy-6-methoxy-8-aminoquinoline (IV). The base (IV) was found to have approximately the same melting point as that reported by Jacobs and Heidelberger[4] for a sample prepared by a similar hydrolysis of 5,8-diamino-6-methoxyquinoline; for confirmation, the diacetyl derivative of IV was prepared and compared, by means of melting

(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 University of Illinois.

(2) Euler, *Ber.*, **39**, 1037, 1040, 1042 (1906).

(3) Kaufler and Suchannek, *ibid.*, **40**, 518 (1907).

(4) Jacobs and Heidelberger, THIS JOURNAL, **44**, 1073 (1922).



points and mixed melting points, with that obtained by reduction and acetylation of 5-hydroxy 6-methoxy-8-nitroquinoline (V). The base II also was synthesized independently by the reaction of 5-chloro-6-methoxy-8-nitroquinoline[5] (VI) with aniline followed by reduction of the nitro group. The sample of II so obtained was identical with that prepared from I.

The principal transformations employed in the synthesis and in the structure proof are shown in the accompanying chart. The conversion of II to a substance believed to be 2-methyl-5,6-dihydro-7-phenylamino-8-methoxy-4-imidazo[ij]quinoline[6] (VII) occurred when the acetyl derivative of II was hydrogenated over platinum oxide catalyst.

β-Naphthylamine also was found to react with nitrosobenzene to give the expected quinone anil, which was identified by reduction to 1-phenylamino-2-naphthylamine.

Experimental

Reaction of Nitrosobenzene with 6-Methoxy-8-aminoquinoline.—A mixture of 18 g. of nitrosobenzene, 27 g. of 6-methoxy-8-aminoquinoline, and 150 ml. of *i*-propyl alcohol was heated until all the solid had gone into solution. The solution was diluted with 150 ml. of water and the mixture was allowed to stand for three hours at room temperature. At the end of this time 150 ml. of water was added and the material separated into two layers. The mixture was then allowed to stand overnight at room temperature. The next morning 300 ml. of water was added, and after one hour the mixture was filtered and the precipitate was extracted with boiling petroleum ether (b. p. 85–115°). The petroleum ether solution was cooled and filtered. The red precipitate melting at 125–130° weighed 18.8 g. An additional 5.5 g. was obtained by concentration of the mother liquor to one-fourth of its volume.

Preparation of 5-Phenylamino-6-methoxy-8-aminoquinoline (II).—Reduction of I to II was accomplished by the use of phenylhydrazine, platinum oxide and hydrogen, or stannous chloride and hydrochloric acid. Only the method employing phenylhydrazine is described below.

To a solution of 8 g. of I (m. p. *ca.* 125°) in 100 ml. of toluene (heating was necessary) was added, in small portions with swirling, a solution of 5 ml. of phenylhydrazine in 20 ml. of toluene. The exothermic reaction proceeded with the evolution of a gas. After all the phenylhydrazine solution had been added the bright red color of the mixture had changed to a light brown. The mixture stood at room temperature for one hour and then was cooled in an ice bath and filtered. The yellow precipitate melting at 195–198° weighed 4.85 g. An additional 0.8 g. of slightly lower melting material was obtained from the mother liquor. The two precipitates were combined and recrystallized from toluene. The yield of yellow crystals melting at 203–205° was 4 g. or about 50% of the theoretical.

Anal. Calcd. for $C_{16}H_{15}N_3O$: C, 72.43; H, 5.70. Found: C, 72.64; H, 5.77.

The acetyl derivative melted at 197–198°.

Preparation of 5-Phenylamino-6-methoxy-8-(3-diethylaminopropylamino)-quinoline (III).—A mixture of 8 g. of the amine II, 10 ml. of 3-diethylaminopropyl chloride, 180 ml. of 95% ethanol, 10 ml. of water, and a few crystals of potassium iodide was heated under reflux for forty hours. At the end of this time all the solid had dissolved and the solution had a deep red color. The mixture was neutralized with a 10% solution of sodium hydroxide and added to five times its volume of water. The resulting mixture was filtered and the precipitate was extracted with boiling petroleum ether (b. p. 30–60°). The petroleum ether solution was concentrated at reduced pressure to a volume of 100 ml. and cooled in an ice-bath. The yellow material which precipitated was filtered and the filtrate was concentrated to 25 ml. and again cooled and filtered. The combined product melting at 74–76° weighed 6.3 g. The pure material, obtained by recrystallization from petroleum ether (b. p. 30–60°), melted at 77–78°.

Anal. Calcd. for $C_{23}H_{30}N_4O$: C, 72.98; H, 7.99. Found: C, 73.22; H, 8.11.

Some of the original amine II (2.1 g.) was recovered from the portion which was insoluble in the petroleum ether. The yield was 75% of the theoretical based on the amount of amine which was not recovered.

Alternate Synthesis of 5-Phenylamino-6-methoxy-8-aminoquinoline (II) from 5-Chloro-6-methoxy-8-nitroquinoline.—A mixture of 2 ml. of aniline and 1 g. of 5-chloro-6-methoxy-8-nitroquinoline was heated at 130–135° for one and one-half hours. The mixture was then cooled and dissolved in hot 95% ethanol. The mixture was made basic with a 10% solution of sodium hydroxide and cooled. The orange crystals that formed were dissolved in hot benzene. When cooled the yellow benzene solution deposited orange crystals which melted at 171–175° and weighed 0.8 g. This product was recrystallized several times from benzene to give the pure material melting at 176–178°.

Anal. Calcd. for $C_{16}H_{13}N_3O_3$: C, 65.08; H, 4.44. Found: C, 65.20; H, 4.36.

This nitro compound was dissolved in ethanol and hydrogenated over platinum oxide catalyst; the product

(5) This compound was kindly supplied by Dr. R. A. Bauman.

(6) Ring Index No. 1584 (28).

melted at 203–205° and the mixed melting point with II showed no depression. The acetyl derivative melted at 197–198° and the mixed melting point with the acetyl derivative of II showed no depression.

Preparation of 5-Hydroxy-6-methoxy-8-aminoquinoline (IV).—A mixture of 0.77 g. of II, 10 ml. of concentrated hydrochloric acid, and 10 ml. of water was heated under reflux for thirty minutes. The mixture was then cooled in an ice-bath and filtered. The filtrate was concentrated to one-fourth of its volume, cooled and filtered. The precipitates were combined and recrystallized from 95% ethanol containing a little concentrated hydrochloric acid. The yellow crystals darkened at 170° and melted with decomposition at 235–240°.

Anal. Calcd. for $C_{10}H_{12}N_2O_2Cl_2$ (dihydrochloride): C, 45.69; H, 4.60. Found: C, 45.95; H, 4.90.

The free base obtained by treatment of the dihydrochloride with aqueous sodium acetate darkened at 130° and melted at 179–181°; the melting point is in good accord with that (180–183°) found by Jacobs and Heidelberger.[4]

For the preparation of 5-acetoxy-6-methoxy-8-acetylaminoquinoline, a mixture of the dihydrochloride of IV, acetic anhydride, and a little pyridine was heated on a steam-bath for ten minutes and then poured into four times its volume of water. The mixture was made basic with ammonium hydroxide and cooled in an ice-bath. The precipitate was collected and recrystallized from a 50–50 alcohol–water solution. The white crystals melted at 162°.

Anal. Calcd. for $C_{14}H_{14}N_2O_4$: C, 61.31; H, 5.15. Found: C, 61.62; H, 5.31.

5-Acetoxy-6-methoxy-8-acetylaminoquinoline was prepared also from 5-hydroxy-6-methoxy-8-nitroquinoline. A solution of the nitro compound in acetic acid and acetic anhydride was heated on a steam-bath. Zinc dust was added in small portions with swirling until the red color disappeared. The mixture was filtered and the filtrate poured into three times its volume of water and cooled. The precipitate was collected and recrystallized from a 50–50 solution of alcohol and water. The product melted at 162° and a mixed melting point with the sample prepared above showed no depression.

Preparation of 2-Methyl-5,6-dihydro-7-phenylamino-8-methoxy-4-imidazo[ij]quinoline[6] (VII).—A mixture of 2.86 g. of the acetyl derivative of II, 150 ml. of acetic acid and 0.1 g. of platinum oxide was subjected to hydrogenation under about three atmospheres pressure. The reaction was carried out at room temperature and was allowed to proceed overnight. The filtrate after removal of the catalyst was evaporated nearly to dryness and the residue was diluted with water and made basic with aqueous ammonia. The precipitate that formed was collected and recrystallized from methanol; the product weighed 1.5 g. and melted at 218–220°. The analytical sample, recrystallized several times from ethanol, melted at 222–224°.

Anal. Calcd. for $C_{18}H_{19}N_3O$: C, 73.70; H, 6.53. Found: C, 73.83; H, 6.39.

Preparation of 1-Phenylamino-2-naphthylamine.—A mixture of 8.56 g. of nitrosobenzene, 11.44 g. of β-naphthylamine, and 140 ml. of isopropyl alcohol was heated until all the solid had dissolved. This solution was allowed to stand at room temperature for one hour and then 300 ml. of water was added. This mixture stood overnight at room temperature. The alcohol solution was decanted from the heavy oil in the bottom of the flask. This oil was then extracted with hot petroleum ether (b. p. 80–110°). The petroleum ether solution was concentrated at reduced pressure and the residue taken up in hot ethanol (95%) and filtered. The filtrate was hydrogenated over platinum oxide catalyst until no more hydrogen was absorbed. The catalyst was removed by filtration and the filtrate concentrated to dryness under reduced pressure. Part of the black oily residue was removed and dissolved in warm ethanol. On cooling a solid precipitated which, after recrystallization from ethanol, melted at 168–170°. An alcohol solution of this solid exhibited fluorescence. The remaining black oil was treated with acetic anhydride and a little pyridine and heated on a steam-bath for ten minutes. This solution was then added to five times its volume of water and a red oil separated. The water solution was decanted and the red oil was dissolved in warm ethanol. Water was added to this solution until a precipitate appeared and the mixture was cooled in an ice-bath. The crystals were collected on a filter and recrystallized from ethanol. The pure compound melted at 200–202°.

Anal. Calcd. for $C_{16}H_{16}N_2O$: C, 78.23; H, 5.84. Found: C, 77.97; H, 5.88.

Noelting, Grandmougin, and Freimann[7] reported the free base to melt at 170° and the acetyl derivative at 200°.

Summary

The synthesis of unsymmetrical diarylamines by condensations of aromatic nitroso compounds has been studied.

5-Phenylamino-6-methoxy-8-(3-diethylaminopropylamino)-quinoline has been prepared by the condensation of nitrosobenzene with 6-methoxy-8-aminoquinoline, reduction of the condensation product with phenylhydrazine, and alkylation of the primary amino group with 3-diethylaminopropyl chloride.

The structure of the reduction product was proved by degradation and by an alternative synthesis from 5-chloro-6-methoxy-8-nitroquinoline and aniline.

β-Naphthylamine also was found to react with nitrosobenzene to give a quinone derivative. Reduction converted the product to 1-phenylamino-2-naphthylamine.

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(7) Noelting, Grandmougin and Freimann, *Ber.*, **42**, 1380 (1909).