This was shaken with 200 cc. of water plus 200 cc. of chloroform, and the purple colored crystals filtered off and dried; wt., 11 g.

Anal. Calcd. for $C_{19}H_{18}N_2 \cdot HCl$: Cl, 11.41. Found: Cl, 11.48.

Summary

1. A satisfactory procedure for the preparation, in good yield, of 2-(*p*-dialkylaminostyryl)-quinoline derivatives is described; some properties of ten new members of this class are reported.

2. The preparation and properties of *p*-dimethylaminobenzylidene diquinaldine are given.

3. 2-(*p*-Dimethylaminostyryl)-quinoline is unaffected by 3 *N* hydrochloric acid during four hours at 100° or by concentrated hydrochloric acid during fifty-five days at room temperature; it reacts with methyl iodide to give a dimethiodide (in addition to the two monomethiodides previously reported).

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[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

Derivatives of Benzo(h)quinoline

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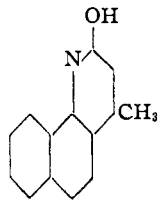
Several series of benzoquinolines have been prepared in this laboratory and studied as intermediates for possible antimalarials.[2] In this investigation benzo(h)quinoline-4-carboxylic acid (VII) was synthesized and from it some aminoketones and carbinolamines were prepared.

2-Chloro-4-methylbenzo(h)quinoline (II)[3] was prepared from the corresponding hydroxy compound (I) by refluxing with a mixture of phos-



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phorus oxychloride and phosphorus pentachloride. Reduction of (II) by tin and hydrochloric acid according to the method of Mikhailov[4] for the corresponding quinoline compound gave 4-methylbenzo(h)quinoline (III). Conversion of (II) to (III) was also effected by hydriodic acid and red phosphorus at 170–180°. Benzo(h)quinoline-4-aldehyde (IV) was obtained by the oxidation of (III) using selenium dioxide. When (IV) was treated with neutral potassium permanganate the corresponding acid (VII) resulted.

A better method of preparing (VII) involved treatment of (III) with benzaldehyde and fused zinc chloride to give 4-styrylbenzo(h)quinoline (VI). By the oxidation of (VI) with potassium permanganate in aqueous pyridine (VII) was produced. The methods used were similar to those employed by Rabe, *et al.*,[5] in the quinoline series. 4 - (*p* - Dimethylaminostyryl) - benzo(h)quinoline (V) was also prepared by the action of fused zinc chloride and *p*-dimethylaminobenzaldehyde on (III).

Benzo(h)quinoline-4-carbonyl chloride hydrochloride (VIII) was prepared by treatment of (VII) with thionyl chloride. Analyses were not carried out on (VIII) but it was converted to 4-carbomethoxybenzo(h)quinoline (IX) and benzo(h)quinoline-4-carboxamide (X). Using a method similar to that employed by Braz[6] in the preparation of 9-acridyl halomethyl ketones, 4-diazoacetylbenzo(h)quinoline (XI) was prepared by the action of (VIII) on an ethereal solution of diazomethane. When (XI) was treated with concentrated hydrochloric acid, 4-benzo(h)quinolyl chloromethyl ketone (XII) resulted. In a similar manner, (XI) and 48% hydrobromic acid gave 4-benzo(h)quinolyl bromomethyl ketone (XIII).

Morpholine and piperidine condensed with (XII) to give 4-benzo(h)quinolyl morpholinomethyl ketone (XIV) and 4-benzo(h)quinolyl piperidinomethyl ketone (XV), respectively, but the yields were low. The latter ketone (XV) was also prepared in poor yields from (XIII) and piperidine. The condensations were carried out in an anhydrous solvent like chloroform or benzene using two moles of the amine and one mole of the halomethyl ketone similar to the procedure employed by King and Work[7] with quinoline compounds. Reduction of (XV) with a palladium on charcoal catalyst under three atmospheres of hydrogen gave α-(4-benzo(h)quinolyl)-β-piperidinoethanol dihydrochloride (XVI).

Another method of synthesizing the acid (VII) was also investigated. This series of reactions has been developed for the preparation of quininic acid by Thielepape and Fulde.[8]

N-Methyl-N-(1-naphthyl)-acetamide, prepared by acetylation of 1-naphthylamine and subsequent N-methylation with sodium and methyl

(1) Parke, Davis and Company Fellow.

(2) Clem and Hamilton, THIS JOURNAL, **62**, 2349 (1940); Untermohlen and Hamilton, *ibid.*, **63**, 156 (1941); Barnum and Hamilton, *ibid.*, **64**, 540 (1942); Mueller and Hamilton, *ibid.*, **65**, 1017 (1943); **66**, 860 (1944); Gerhardt and Hamilton, *ibid.*, **66**, 479 (1944).

(3) Gibson, *et al.*, *J. Chem. Soc.*, 2247 (1926).

(4) Mikhailov, *J. Gen. Chem.* (U. S. S. R.), **6**, 511 (1936); *C. A.*, **30**, 6372 (1936).

(5) Rabe, *et al.*, *Ber.*, **64B**, 2487 (1931).

(6) Braz, *J. Gen. Chem.* (U. S. S. R.), **11**, 851 (1941); *C. A.*, **36**, 4122 (1942).

(7) King and Work, *J. Chem. Soc.*, 1307 (1940); 401 (1942).

(8) Thielepape and Fulde, *Ber.*, **72B**, 1432 (1939).

iodide, was condensed with diethyl oxalate giving α-ethoxalyl-N-methyl-N-(1-naphthyl)-acetamide (XVII).

No further work was done on this series.

Experimental

2-Chloro-4-methylbenzo(h)quinoline (II).—A mixture of 200 g. (0.95 mole) of (I), 400 ml. of phosphorus oxychloride and 225 g. of phosphorus pentachloride was refluxed for six to seven hours and then the phosphorus oxychloride was removed by reduced pressure distillation. The residual phosphorus halides were decomposed with ice and the solid residue was dissolved in 600 ml. of 12 *N* hydrochloric acid and the solution filtered free of some tarry material. The product was precipitated by the addition of the acid solution to four liters of water and recrystallized from ethanol; pale tan needles of m. p. 134–136°; yield, 138 g. (64%). Gibson, *et al.*, give a m. p. of 135–136°.[8]

4-Methylbenzo(h)quinoline (III).—A suspension of 60 g. (0.26 mole) of (II) and 45 g. of mossy tin in 400 ml. of water containing 300 ml. of 12 *N* hydrochloric acid and 575 ml. of ethanol was refluxed until complete solution was effected (15–16 hours). The solution was then decanted from a small amount of undissolved tin and concentrated by distillation to about one-half of its volume to remove most of the ethanol. A stannous chloride addition compound of (III) crystallized on cooling. The mixture was made alkaline with sodium hydroxide and the product was extracted with ether. Removal of the ether, treatment with charcoal and crystallization from ethanol gave a white crystalline product of m. p. 77–78°; yield, 37 g. (73%).

Anal. Calcd. for $C_{14}H_{11}N$: C, 87.01; H, 5.74. Found: C, 86.69, 86.96; H, 6.07, 6.11.

Benzo(h)quinoline-4-aldehyde (IV).—To a stirred solution of 3.0 g. (0.015 mole) of (III) in 60 ml. of xylene, heated in an oil-bath to 130–135°, was added, over a period of thirty minutes, 2.6 g. of selenium dioxide. Stirring and heating was continued for an additional hour and, after cooling, the mixture was filtered free of black selenium. Steam distillation of the xylene gave a yellowish-brown oil which solidified on cooling. Recrystallization from 50–60% ethanol gave a light tan crystalline product of m. p. 126–127°. (IV) gives a positive Tollens test and a red precipitate with phenylhydrazine; yield, 0.3 g. (10%).

Anal. Calcd. for $C_{14}H_{9}NO$: C, 81.14; H, 4.38. Found: C, 81.16, 81.24; H, 4.77, 4.72.

4-(*p*-Dimethylaminostyryl)-benzo(h)quinoline (V).—A stirred mixture of 5 g. (0.026 mole) of (III), 3.86 g. of *p*-dimethylaminobenzaldehyde and 3.6 g. of fused zinc chloride was heated by means of an oil-bath at 135–140° for four hours. The cooled mixture was triturated with dilute ammonium hydroxide and extracted with ether. The combined yellow ether extracts were dried over anhydrous sodium sulfate and, on concentrating the ether solution, the yellow crystalline product separated. Recrystallization from acetone gave bright yellow crystalline (V) of m. p. 183.5–184°; yield, 3 g. (36%).

Anal. Calcd. for $C_{23}H_{20}N_2$: C, 85.15; H, 6.22. Found: C, 85.16, 85.15; H, 6.50, 6.39.

4-Styrylbenzo(h)quinoline (VI).—A mixture of 34 g. (0.176 mole) of (III), 155 ml. of benzaldehyde and 37 g. of fused zinc chloride was refluxed gently with constant stirring for six hours. After cooling, the yellow zinc chloride addition compound of (VI) was filtered and washed well with ether. Free (VI) was liberated by triturating with dilute ammonium hydroxide and then recrystallized from acetone; pale yellow needles of m. p. 139–140°; yield, 36.5 g. (74%).

Anal. Calcd. for $C_{21}H_{15}N$: C, 89.65; H, 5.37. Found: C, 89.21, 89.44; H, 5.49, 5.39.

Benzo(h)quinoline-4-carboxylic Acid (VII).—To a stirred solution of 42.5 g. (0.151 mole) of (VI) in 300 ml. of pyridine containing 60 ml. of water was added, over a period of one hour, 63.6 g. of potassium permanganate. The temperature was kept below 20°. During this time 175 ml. of water was added to prevent solidification due to precipitated manganese dioxide. Stirring was continued for another thirty minutes and then the reaction mixture was made definitely alkaline with sodium hydroxide and filtered free of manganese dioxide. The filtrate was diluted to 3.5 liters with water and the product was precipitated by acidification of the hot solution with hydrochloric acid. Repeated precipitation of (VII) from the hot solution of its sodium salt gave pure (VII) which when recrystallized from dilute acetic acid melted at 281–282°; yield, 28 g. (83%). Mumm, *et al.*,[9] give a m. p. of 278°.

The acid (VII) was also produced from the aldehyde (IV). To a solution of 40 mg. of (IV) in three ml. of acetone (40°) was added dropwise with stirring 0.55 ml. of a 5% aqueous solution of potassium permanganate. The temperature was maintained at 40° for an additional 15 minutes and then sulfur dioxide was passed through the mixture to reduce the manganese dioxide. The clear yellow solution was then heated over a water-bath, maintaining the volume by addition of water. Recrystallization of the resulting solid from dilute acetic acid gave yellow crystals of m. p. 281–282°; yield, 35 mg. (85%). Samples of (VII) from both (VI) and (IV) gave no depression of the m. p. when mixed.

Benzo(h)quinoline-4-carbonyl Chloride Hydrochloride (VIII).—A mixture of 28 g. (0.125 mole) of (VII) and 110 ml. of thionyl chloride was refluxed for thirty minutes and then the excess thionyl chloride was removed by reduced pressure distillation. The product was filtered, washed with dry benzene and dried in a vacuum desiccator over potassium hydroxide; yield, 34 g. (almost quantitative) of yellowish-orange (VIII).

4-Carbomethoxybenzo(h)quinoline (IX).—Two grams (0.0072 mole) of (VIII) and 40 ml. of absolute methanol were refluxed for 1.5 hours and after cooling, the hydrochloride of (IX) was filtered and the free ester liberated with dilute sodium bicarbonate solution. Recrystallization from methanol gave white needles of m. p. 99–100°; yield, 1.4 g. (82%).

Anal. Calcd. for $C_{15}H_{11}NO_2$: C, 75.93; H, 4.67. Found: C, 75.80, 75.97; H, 4.89, 4.83.

Benzo(h)quinoline-4-carboxamide (X).—Two grams (0.0072 mole) of (VIII) was added slowly with stirring to 25 ml. of ice-cold concentrated ammonium hydroxide. The resulting white solid was recrystallized from ethanol; white needles of m. p. 226–227.5°; yield, 1.1 g. (69%).

Anal. Calcd. for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54. Found: C, 75.53, 75.60; H, 4.73, 4.76.

4-Diazoacetylbenzo(h)quinoline (XI).—To an ice-cold ethereal solution of diazomethane (approx. 0.1 mole), which was prepared from 14.5 g. of nitrosomethylurea,[10,11] was added with constant stirring 7.7 g. (0.028 mole) of (VIII) (twenty minutes). Stirring and cooling was continued for three hours and then the product was obtained by filtration and concentration of ether solution: pale yellow crystals from ether or petroleum ether of m. p. 110.5–112°; yield, 6.3 g. (90%).

Anal. Calcd. for $C_{15}H_{9}N_3O$: C, 72.86; H, 3.67. Found: C, 72.69, 72.89; H, 3.80, 3.93.

4-Benzo(h)quinolyl Chloromethyl Ketone (XII).—To 45 ml. of 12 *N* hydrochloric acid was slowly added with stirring 6.3 g. (0.025 mole) of (XI). When evolution of nitrogen was completed, the mixture was diluted to four times its volume with water. Free (XII) was liberated with ice-cold dilute sodium hydroxide. Recrystallization from acetone gave pale yellow needles of m. p. 171–172°; yield, 5.9 g. (91%).

Anal. Calcd. for $C_{15}H_{10}ClNO$: C, 70.45; H, 3.94. Found: C, 70.62, 70.28; H, 4.22, 4.13.

(9) Mumm, *et al.*, *Ann.*, **514**, 34 (1934).

(10) Arndt, Loewe and Avan, *Ber.*, **73B**, 606 (1940).

(11) Arndt, "Organic Syntheses," **15**, 3 (1935).

4-Benzo(h)quinolyl Bromomethyl Ketone (XIII).—To 25 ml. of 48% hydrobromic acid was added slowly with stirring 3.0 g. (0.012 mole) of (XI). The procedure was similar to that for (XII). Recrystallization from acetone gave pale yellow needles of m. p. 154.5–155°; yield, 3.2 g. (88%).

Anal. Calcd. for $C_{15}H_{10}BrNO$: C, 60.02; H, 3.36. Found: C, 60.12, 60.23; H, 3.42, 3.44.

4-Benzo(h)quinolyl Morpholinomethyl Ketone (XIV).—A mixture of 50 ml. of chloroform, 2.40 ml. (0.027 mole) of morpholine and 3.38 g. (0.013 mole) of (XII) was refluxed for four hours. On cooling there was obtained 0.65 g. of morpholine hydrochloride and from the filtrate by addition of 70 ml. of dry ether, another 0.65 g. of morpholine hydrochloride. The filtrate was evaporated under reduced pressure and the crude product was precipitated by the addition of absolute ethanol. Recrystallization from chloroform gave pale yellow crystalline (XIV) of m. p. 209–210°; yield, 0.7 g. (17%).

Anal. Calcd. for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92. Found: C, 74.25, 74.21; H, 5.61, 5.64.

4-Benzo(h)quinolyl Piperidinomethyl Ketone (XV).—To a solution of 1.18 ml. (0.0118 mole) of piperidine in 20 ml. of dry benzene was added 1.5 g. (0.0059 mole) of (XII) (ten minutes). After gentle shaking for three hours, 0.65 g. of piperidine hydrochloride was collected by filtration. By concentration of the filtrate under reduced pressure and addition of absolute ethanol, the crude product was precipitated. Recrystallization from absolute ethanol containing a small amount of chloroform and subsequent drying in a vacuum oven at 100° for 18 hours gave bright yellow needles of m. p. 183–185°; yield, 0.6 g. (33%).

To a suspension of 1.0 g. (0.0033 mole) of (XIII) in 10 ml. of dry benzene was added a solution of 0.69 ml. (0.0068 mole of piperidine in 10 ml. of dry benzene (twenty minutes). Gentle shaking was continued for an additional ten minutes and then 0.5 g. of piperidine hydrobromide was removed by filtration. The remaining procedure was similar to the above. There was obtained bright yellow needles of m. p. 183–185°; yield, 0.36 g. (35%). Mixtures of (XV) obtained from (XII) and (XIII) exhibited no m. p. depression when mixed.

Anal. Calcd. for $C_{20}H_{20}N_2O$: C, 78.92; H, 6.62. Found: C, 79.21, 79.18; H, 6.52, 6.36.

The low yields of aminoketones seemed to be due to a competing reaction involving the intramolecular elimination of hydrogen halide from the halomethyl ketone. When the bromoketone (one mole) was shaken with triethylamine (two moles) in dry benzene, a considerable quantity of triethylamine hydrobromide was isolated.

α-(4-Benzo(h)quinolyl)-β-piperidinoethanol Dihydrochloride (XVI).—A solution of nine-tenths gram of (XV) in 50 ml. of water containing 25 ml. of 95% ethanol and three ml. of 12 *N* hydrochloric acid was shaken under three atmospheres pressure of hydrogen at room temperature in the presence of a palladium on charcoal catalyst (four hours). The catalyst was removed by filtration and most of the ethanol by evaporation under reduced pressure. The free base of (XVI) was precipitated as a white solid by the addition of dilute base and then extracted with ether and the ether extracts dried with anhydrous sodium sulfate. By the addition of absolute ethanolic hydrogen chloride to the ether solution, (XVI) was precipitated. Recrystallization from absolute ethanol containing a small amount of dry methanol gave white crystalline (XVI) of m. p. 230–232°; yield, 0.4 g. (45%).

Anal. Calcd. for $C_{20}H_{24}Cl_2N_2O$: C, 63.32; H, 6.38. Found: C, 63.06, 63.45; H, 6.64, 6.33.

α-Ethoxalyl-N-methyl-N-[1-naphthyl]acetamide (XVII).—To a stirred mixture of 0.6 g. of sodium (small pieces) in 20 ml. of sodium-dried ether was added 1.46 ml. (0.025 mole) of absolute ethanol. When the initial reaction had subsided, 4.0 ml. (0.029 mole) of diethyl oxalate was added slowly and as soon as all the sodium had dissolved, 5.0 g. (0.025 mole) of N-methyl-N-[1-naphthyl]acetamide was added. The stirred solution was refluxed over a water bath for two hours and the cooled solution was then poured onto a mixture of ice and 1.2 ml. of concentrated sulfuric acid (acid to congo red). The crude product was extracted with ether, and after drying the ether extracts with sodium sulfate and removal of the ether, was recrystallized from petroleum ether (b. p. 70–80°): white crystalline (XVII) of m. p. 88–89°; yield, 3 g. (40%).

Anal. Calcd. for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.73. Found: C, 68.25, 68.20; H, 5.77, 5.72.

Summary

The preparation of benzo(h)quinoline-4-carboxylic acid is described. From the corresponding acid chloride hydrochloride, 4-carbomethoxybenzo(h)quinoline, benzo(h)quinoline-4-carboxamide and 4-diazoacetylbenzo(h)quinoline were prepared. From the latter compound, 4-benzo(h)quinolyl chloromethyl and 4-benzo(h)quinolyl bromoethyl ketones were synthesized in good yields.

Morpholine and piperidine condensed with these halomethyl ketones in poor yields to give 4-benzo(h)quinolyl morpholinomethyl and 4-benzo(h)quinolyl piperidinomethyl ketones, respectively. From the latter aminoketone, α-(4-benzo(h)quinolyl)-β-piperidinoethanol dihydrochloride was prepared.

By a Claisen condensation between diethyl oxalate and N-methyl-N-[1-naphthyl]acetamide, α-ethoxalyl-N-methyl-N-[1-naphthyl]acetamide was synthesized.

LINCOLN, NEBRASKA RECEIVED DECEMBER 1, 1944