

After removing most of the solvent on the steam plate, the solution was poured onto an alumina column (Merck). Development and elution with 15% benzene in petroleum ether (60-70°) gave 2 fractions which were subsequently recrystallized from ethanol. The first afforded 400 mg. (17%) of triphenylmethane melting at 92° and not depressed by an authentic sample. The second gave 210 mg. of 9-phenylfluorene melting at 147-148° and not depressed by an authentic sample.<sup>5</sup>

Elution of the column with benzene gave a colorless gum which solidified on treatment with ethanol. The yield of material melting at 160-180° was 700 mg. After several reprecipitations from benzene with ethanol, the melting point of this white amorphous solid was 200-203°. Further efforts at purification or crystallization were fruitless. The material was soluble in all of the common organic solvents except alcohols and acetic acid. It did not dissolve in concentrated sulfuric acid. Oxidation of 900 mg. of the hydrocarbon with chromic acid in acetic acid afforded a few milligrams of benzoic acid melting at 121-122° and undepressed by admixture with an authentic sample.

*Anal.*, Calcd. for (C<sub>15</sub>H<sub>13</sub>)<sub>2</sub>: C, 94.6; H, 5.4. Found: C, 95.03; H, 5.2.

Three cryoscopic molecular weight determinations of V in benzene gave values of 510, 498, and 530. Calcd. for (C<sub>15</sub>H<sub>13</sub>)<sub>2</sub>: mol. wt., 482.6.

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(5) A. Kliegl, *Ber.*, **38**, 287 (1905).

#### 4-(4-Aminostyryl)quinolines<sup>1</sup>

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A series of analogs of 4-(4-dimethylaminostyryl)quinoline (I)<sup>2,3</sup> have been prepared in which other groups have the place of the dimethylamino group. 4-(4-Aminostyryl)quinoline, prepared by two different methods, was a convenient intermediate for the preparation of a variety of derivatives through reactions of the primary amino group. The effectiveness of oral administration of the compounds in causing regression or inhibition of growth of Lymphoma 8 tumors in rats is being tested at the Wistar Institute of Anatomy and Biology through the cooperation of Dr. Margaret Reed Lewis, Dr. Boland Hughes, and Mr. Aubrey L. Bates, and the financial assistance of a grant-in-aid from the National Institutes of Health. Effectiveness of intraperitoneal injection of arachis oil solutions of the compounds in preventing growth of Walker 256 tumors is being tested by Professor Alexander Haddow and his associates at the Chester Beatty

(1) This research was aided by a grant from the American Cancer Society.

(2) H. Gilman and G. Karmas, *J. Am. Chem. Soc.*, **67**, 342 (1945).

(3) M. A. Clapp and R. S. Tipson, *J. Am. Chem. Soc.*, **68**, 1332 (1946).

Research Institute. Most of the compounds reported here were less active than I against the tumors, in that larger doses were necessary in order to produce a given response, but the toxic side effects varied with the compound and method of administration. Some of the compounds had the advantage of being much less toxic than I. A more detailed report of the biological observations is to be made elsewhere.

#### EXPERIMENTAL

4-(4-Diethylaminostyryl)quinoline (II) did not crystallize as readily as I from the still residue obtained by the general method of Clapp and Tipson.<sup>3</sup> Isolation of the product through the zinc salt<sup>4</sup> was more convenient. II was found to be as active as I against Lymphoma 8.<sup>5</sup> The hydrochloride, administered intravenously to leukemic rats, was reported to produce a prompt return of the white blood cell count to normal.<sup>6</sup>

4-(4-Diethylaminostyryl)-3-methylquinoline. Fifty-six grams (0.376 mole) of *p*-diethylaminobenzaldehyde was added to a molten mixture of 10.65 g. (0.078 mole) of zinc chloride and 25 g. of 3-methyllepidine (0.159 mole). After heating 8 hr. in an oil bath at 175-180°, the tarry reaction mixture was dissolved partially in methanol. Red crystals weighing 13.9 g. were separated from the solution. These were ground thoroughly with two portions of ammonium hydroxide, and washed with water. The tar thus produced was dissolved in hot isohexane. The yellow solution was decanted from the red oil that separated on cooling slightly. Cooling the solution to room temperature then precipitated 2.3 g. of solid which was recrystallized from 65 ml. of isohexane to yield 1.9 g., (4%) of yellow crystals, m.p. 104.6-107.1°.<sup>7</sup>

*Anal.* Calcd. for C<sub>22</sub>H<sub>24</sub>N<sub>2</sub>: C, 83.50, H, 7.65. Found: C, 83.66, 83.60; H, 7.72, 7.56.<sup>8</sup>

The *picrate* of this base was obtained as dark red crystals; m.p. 270.0-270.8°.

*Anal.* Calcd. for C<sub>28</sub>H<sub>27</sub>N<sub>5</sub>O<sub>7</sub>: C, 58.10, H, 3.60, N, 14.73. Found: C, 58.33, 57.89; H 3.47, 3.75.<sup>8</sup>

4-[4-(*N*-Ethyl-*N*-methylamino)styryl]quinoline. By the method of Leese<sup>9</sup> a mixture of 27.3 g. (0.21 mole) 4-(*N*-ethyl-*N*-methylamino)benzaldehyde and 30 g. (0.21 mole) of lepidine hydrochloride was heated 30 min. in an oil bath at 150°. The dark purple mass solidified on cooling, and was dissolved in 400 ml. of hot methanol; then 200 ml. of distilled water and 100 ml. of concentrated ammonium hydroxide were added. The yellow-brown crystals that appeared on chilling were triturated with ammonium hydroxide in a mortar, washed with water, and dried; weight, 42.3 g., m.p. 96-99°; after 8 additional recrystallizations from methanol, m.p. 123.7-124.8°, yield 4.4 g. (8.7%).

*Anal.* Calcd. for C<sub>20</sub>H<sub>20</sub>N<sub>2</sub>: C, 83.29, H, 6.99. Found: C, 83.27, 83.44, H, 6.97, 7.17.

4-[4-(*N*-Benzyl-*N*-ethylamino)styryl]quinoline. A mixture of 10 g. (0.07 mole) of lepidine, 16 g. (0.067 mole) of 4-(*N*-benzyl-*N*-ethylamino)benzaldehyde, and 4.8 g. of zinc chloride was heated 24 hr. at 110-120°. The reaction mixture was dissolved in chloroform, washed with ammonium hydroxide, and dried over sodium sulfate. The chloroform

(4) C. T. Bahner, Clarence Cook, John Dale, John Fain, Edgar Franklin, J. C. Goan, William Stump, and Joan Wilson, *J. Org. Chem.*, **22**, 682 (1957).

(5) M. R. Lewis, B. Hughes, and A. L. Bates, *Growth*, **19**, 323 (1955).

(6) B. Hughes, M. R. Lewis, and A. L. Bates, *Nature*, **177**, 331 (1956).

(7) All melting points are corrected.

(8) Analyses by Weiler and Strauss.

(9) C. L. Leese, private communication.

was evaporated, leaving an oil. The oil was dissolved in absolute ethanol. Water was added and a tar separated. The liquid was decanted and the tar was dissolved in 75 ml. of absolute ethanol. After the solution had stood for two months, crystals formed and were filtered off. Six recrystallizations from ethanol and six recrystallizations from isohexane gave 1.9 g. (8%) of yellow crystals, m.p. 110.9–111.4°.

*Anal.* Calcd. for  $C_{28}H_{24}N_2$ : C, 85.68, H, 6.64. Found: C, 85.32, 85.49; H, 6.65, 6.72.<sup>8</sup>

*4-[4-(N-Benzyl-N-ethylamino)styryl]quinoline methiodide.* A solution of 1.00 g. of lepidine methiodide, 1.00 g. of 4-(N-benzyl-N-ethylamino)benzaldehyde, and 3 drops of piperidine in 75 ml. of methanol was boiled 1 hr. and filtered while hot. On chilling, the filtrate deposited dark purple crystals that were recrystallized five times from methanol; m.p. 189–190°, yield 0.31 g. (17%).

*Anal.* Calcd. for  $C_{27}H_{27}N_2I$ : C, 64.03; H, 5.37. Found: C, 64.10, 64.26; H, 5.11, 5.35.<sup>8</sup>

*4-(4-Aminostyryl)quinoline.* Twenty-six grams (0.094 mole) of 4-(4-nitrostyryl)quinoline was mixed with 120 ml. of hydrochloric acid to form a thin paste. This mixture was placed in a 500-ml. 3-necked flask equipped with a condenser and a sealed stirrer, and a solution of 182 g. of tin (II) chloride 2-hydrate in 100 ml. of hydrochloric acid was added. The mixture was refluxed, with stirring, for one hour. Cooling yielded yellow crystals. They were stirred with enough water to make a smooth paste; and then 800 ml. of 10% sodium hydroxide was added with mechanical stirring. The crystals were recovered by filtration, dried with warm air, extracted with isohexane in a Soxhlet extractor, and recrystallized three times from isopropyl alcohol and once from benzene to yield 15.3 g. of yellow crystals, m.p. 152.4–154.0°. Concentration of the mother liquors yielded another 1.5 g. of compound. The total yield was 16.8 g. (73%).

*Anal.* Calcd. for  $C_{17}H_{14}N_2$ : C, 82.90, H, 5.73. Found: C, 83.07, 82.76; H, 5.73, 5.77.<sup>10</sup>

This compound was prepared also from *p*-acetamidobenzaldehyde. Sixty-eight grams (0.5 mole) of zinc chloride and 143 g. (1 mole) of lepidine were mixed to form a white solid. Then 245 g. (1.5 mole) of *p*-acetamidobenzaldehyde was added and the mixture was heated at 180°, with frequent stirring until all the solid dissolved. At the end of 2.5 hr. lumps of red dough-like material were removed while hot. When they had cooled they were ground and then washed by boiling with one 400-ml. portion of methanol and two 500-ml. portions of methanol. The red residue, after drying in an oven, weighed 206 g. (58%). A 200-g. portion of this zinc salt was stirred for 40 min. with 1 liter of 7.5*N* ammonium hydroxide. The solid was separated by filtration, washed with water, and boiled 2 hr. with 1250 ml. of 4.8*N* hydrochloric acid. When all the solid had dissolved, the solution was heated another 15 min., allowed to cool to room temperature, and made basic with ammonium hydroxide. The yellow crystals which formed were filtered, washed with water, and dried in an oven at 100°. They were then extracted with one liter of benzene in a Soxhlet extractor; yield 75 g., m.p. 152–154°. They were shown to be genuine 4-(4-aminostyryl)quinoline by mixed melting point comparison with an analyzed sample made by reduction of 4-(4-nitrostyryl)quinoline. Reducing the volume of the mother liquor by distillation yielded successive batches weighing 18.5 g., m.p. 151.0–152.7°; 10 g., m.p. 151.6–153.3° and 2 g. The combined first and second methanol washings mentioned above were treated with 25 g. of zinc chloride in 50 ml. of methanol. A sticky mass separated which gradually changed into 114 g. of dark red crystals. There were treated in the same manner as the others to yield 17 g. of product, m.p. 150.7–152.4°. The total yield was 122.5 g. (50%).

*4-(4-Formamidostyryl)quinoline.* Twenty grams (0.0813 mole) of 4-(4-aminostyryl)quinoline and 200 ml. of 90%

formic acid were refluxed for 40 min. The reaction mixture was cooled in an ice bath and stirred mechanically. The mixture was chilled 1 hr.; then it was filtered and the yellow crystals were washed with six 50-ml. portions of water. Three recrystallizations from methanol (15 ml./g.) gave yellow crystals that softened at 159° and melted at 162.5–164.1°, yield (85%).

*Anal.* Calcd. for  $C_{18}H_{14}N_2O$ : C, 78.81, H, 5.14. Found: C, 78.61, 78.71; H, 5.06, 5.17.<sup>8</sup>

*N,N'-Bis[4-(4-quinolyl)styryl]formamidine.* A solution of 12.0 g. (0.0488 mole) of 4-(4-aminostyryl)quinoline and 7.2 ml. of ethyl orthoformate in 140 ml. of absolute ethanol was refluxed 6 hr. This mixture was chilled 40 min. and filtered to yield 5.7 g. of yellow crystals. The mother liquor was allowed to stand for two days, after which filtration yielded another 1.35 g. of product. No more crystals were produced when the mother liquor was refluxed another 5.5 hr., but addition of 4 ml. of ethyl orthoformate, refluxing 3 hr., and standing overnight, yielded 3.5 g. more. Adding another 3 ml. of ethyl orthoformate to the mother liquor and refluxing 8 hr. gave no more compound. When the product proved only slightly soluble in hot ethyl acetate, alcohols, ether, and benzene, it was purified by extraction with benzene in a Soxhlet extractor. The benzene was filtered at room temperature and the crystals were dried 30 min. at 110°: yield 7.60 g., m.p. 224–225°, (softening at 220°).

*Anal.* Calcd. for  $C_{35}H_{28}N_4$ : C, 83.64, H, 5.21. Found: C, 83.55, 83.32; H, 5.13, 5.18.<sup>8</sup>

An additional 0.85 g. of the product was obtained from the mother liquors by concentrating and chilling them. Total yield 8.45 g. (69%).

*4-(4-Carbamidostyryl)quinoline.* Fifteen grams (0.0609 mole) of 4-(4-aminostyryl)quinoline was dissolved in 91 ml. of acetic acid, 60 ml. of water, and 2 ml. of hydrochloric acid. The solution was cooled in an ice bath, and 7.0 g. of potassium cyanate in 10 ml. of water was added. The solution was allowed to stand 45 hr.; then a small amount of precipitate was filtered from the solution and the filtrate was added dropwise to 150 ml. of ammonium hydroxide cooled by an ice bath and stirred mechanically. The yellow precipitate was filtered off and washed with four 75-ml. portions of water. The moist precipitate was boiled 30 min. with 600 ml. of benzene. The mixture was filtered hot, yielding 11.5 g. of brownish crystals and a yellow filtrate. The brownish crystals were recrystallized from a mixture of 200 ml. of ethanol and 500 ml. of benzene to yield 2.3 g. of pale yellow crystals. These were recrystallized by extraction with 300 ml. of benzene in a Soxhlet extractor, to yield 2.12 g. of white crystals (12%), m.p. 262–266° dec. (darkening from 220°).

*Anal.* Calcd. for  $C_{18}H_{15}N_3O$ : C, 74.72, H, 5.23. Found: C, 74.67, 74.67, 74.68; H, 5.24, 5.24, 5.28.<sup>8</sup>

*4-[4-(Carbethoxyamino)styryl]quinoline.* A solution of 10.0 g. (0.084 mole) of 4-(4-aminostyryl)quinoline and 8 ml. (0.084 mole) of ethyl chloroformate in 200 ml. of chloroform was refluxed 1.5 hr., then placed in the freezer. The 13.7 g. of reddish brown crystals were triturated with two successive 50-ml. portions of water. Filtration then yielded yellow crystals which, after drying for five days over Drierite, weighed 11.8 g. Six recrystallizations from benzene (25 ml./g. of compound), and drying 5 hr., at 100° at 0.4 mm, gave 7.0 g. (55%) of yellow crystals, m.p. 151.7–152.4°, (softens at 150.3°).

*Anal.* Calcd. for  $C_{20}H_{18}N_2O_2$ : C, 75.45, H, 5.70. Found: C, 75.50, 75.55; H, 5.75, 5.85.<sup>10</sup>

*4-[4-(Dimethylaminobenzal)amino]styryl]quinoline.* Nine grams (0.0366 mole) of 4-(4-aminostyryl)quinoline and 5.49 g. (0.0368 mole) of *p*-dimethylaminobenzaldehyde were ground together in a mortar. The mixture was heated 1.5 hr. in an oven at 110°. The hard porous mass which formed was crushed to a powder and recrystallized from 1050 ml. of ethyl acetate. A second recrystallization from 900 ml. of ethyl acetate yielded 10.90 g. of light orange crystals, m.p. 194–195.5°.

