## [Contribution from the Department of Research in Pure Chemistry, Mellon Institute of Industrial Research]

## Studies in the Quinoline Series. III. Some Derivatives of 4-Styrylquinoline<sup>1</sup>

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The preparation and properties of a number of 2-(p-dialkylaminostyryl)-quinolines have been described recently<sup>2</sup>; we now present a study of some of the 4-(p-dialkylaminostyryl) derivatives. Since the methyl group at position 4 is less reactive<sup>3</sup> than that at position 2, the modification of Brahmachari's method previously described<sup>2</sup> could not be applied to the preparation of the substituted 4-styryl derivatives. However, we were able to isolate them by treating the appropriate lepidine derivative with an excess of aldehyde at 180° during six hours, in the presence of an-hydrous zinc chloride.

In previous communications<sup>4</sup> from this Department it has been shown that the introduction of a hydroxyethyl group into the molecule of certain drugs greatly diminishes the toxicity, a principle which led to the discovery<sup>5</sup> of 6-hydroxyethyl-apocupreine. For synthetic experiments in the quinoline series, it therefore became desirable to prepare 6-hydroxyethoxylepidine, a substance related to the quinoline moiety of this drug. Its formation has now been achieved by hydrolysis of 6-methoxylepidine to the 6-hydroxy derivative, followed by alkylation by means of benzyloxyethyl p-toluenesulfonate and subsequent debenzylation.

We have also studied the demethylation of some styryl derivatives of 6-methoxyquinoline and the preparation of the 6-hydroxyethyl ethers.

We take this occasion to describe the preparation of two 2-(p-dialkylaminoanilino) derivatives of 6-methoxylepidine. In addition, treatment of 2-hydroxy-6-methoxylepidine with p-acetylaminobenzenesulfonyl chloride in pyridine gave a substance having the correct analysis for 2-(pacetaminobenzenesulfonyloxy)-6-methoxylepidine.

## Experimental

**6-Hydroxylepidine.**—The following method is superior to that described by Koenigs.<sup>6</sup> A solution of distilled 6-methoxylepidine (10 g.) in 100 cc. of 60% sulfuric acid was boiled gently under reflux in a bath at  $150-160^{\circ}$  for four hours (reaction temp.,  $135-137^{\circ}$ ). The brown solution was then allowed to cool to room temperature, giving a whitish, crystalline mass which was dissolved in 200 cc. of water and made alkaline with 8 N sodium hydroxide (300 cc.). (Addition of the alkali precipitates, at first,

(1) Presented, in part, at the meeting of the Division of Organic Chemistry, American Chemical Society, held in New York, N. Y., September 13, 1944.

(2) Tipson, This Journal, 67, 507 (1945).

(3) Fischer, et al., J. prakt. Chem., 100, 91 (1920); Eibner, Ber., 37, 3605 (1904).

(4) Cretcher and Pittenger, THIS JOURNAL, 47, 2560 (1925); Butler, Nelson, Renfrew and Cretcher, *ibid.*, 57, 575 (1935).

(5) Butler, Renfrew, Cretcher and Souther, *ibid.*, **59**, 227 (1937); Butler and Renfrew, *ibid.*, **60**, 1473 (1938); Tipson, Clapp and Cretcher, *ibid.*, **65**, 1092 (1943).

(6) Koenigs, Ber, 23, 2669 (1890).

some white solid which redissolves as the solution is made strongly alkaline.) This solution was treated with carbon dioxide until faintly alkaline to phenolphthalein, and the colorless, semi-crystalline precipitate filtered off, washed on the filter with water, air-dried, and dried at 60° (twentyfour hours); yield, quantitative; m. p., 222-223°. For recrystallization, 10 g. was dissolved in 120 cc. of boiling absolute ethanol, the hot solution filtered through a fluted filter, the filtrate diluted with 120 cc. of water and kept overnight in a refrigerator; wt. of colorless crystals, 8.6 g.; m. p., 222 to 224° (Koenigs<sup>6</sup> gave m. p., 216-218°). Anal. Calcd. for C<sub>10</sub>H<sub>9</sub>NO: C, 75.43; H, 5.7; N, 8.81. Found: C, 75.40; H, 6.1; N, 8.80. Benzylowyethyl  $\leftarrow$  tohuenesulforate was proposed by the

Benzyloxyethyl p-toluenesulfonate was prepared by the general method outlined by Tipson<sup>7</sup>; total yield of crude, crystalline ester, 75% of the theoretical; m. p., 45°. It was recrystallized by dissolving 10 g. in 40 cc. of dry ether, giving 8.3 g. of colorless crystals, m. p., 45° Anal. Calcd. for C<sub>16</sub>H<sub>18</sub>O<sub>4</sub>S: S, 10.47. Found: S, 10.40. Addition of 2 volumes of pentane to the mother liquor gave a second crop (1 g.) of colorless crystals; m. p., 45°.

6-Benzyloxyethoxylepidine.--- To a warm solution of 10 g. of recrystallized 6-hydroxylepidine in 120 cc. of absolute ethanol, 4.2 g. of 85% potassium hydroxide dissolved in 40 cc. of absolute ethanol was added in portions with shaking; 19.3 g. of crystalline benzyloxyethyl p-toluenesulfonate was now added and the solution heated under reflux in a boiling water-bath during three hours. The alkylation product was isolated in the usual manner,5 giving 16.8 g. (91%) of dark-brown, sweet-smelling sirup. All attempts to crystallize the product were without Crude 6-benzyloxyethoxylepidine (16.7 g.) was success. purified by extraction with 1500 cc. of boiling heptane under reflux, 1.0 g. of purple-black gum remaining un-The extract was evaporated under diminished dissolved. pressure, giving a yellow-brown sirup which was extracted with 100 cc. of boiling hexane, yielding 13.4 g. of undissolved pale yellow sirup. Anal. Calcd. for  $C_{19}H_{19}NO_2$ : C, 77.77; H, 6.5; N, 4.78. Found: C, 77.22; H, 6.6; N, 4.52.

**6-Hydroxyethoxylepidine.**—Purified 6-benzyloxyethoxylepidine (10.5 g.) was dissolved in 1,050 cc. of 3 N hydrochloric acid and the solution heated in a boiling waterbath for six hours; it was then allowed to cool to room temperature, extracted twice with 250 cc. of 96% ether, and the aqueous layer made alkaline with 8 N sodium hydroxide and extracted three times with chloroform. The chloroform extract was washed, dried, filtered, and evaporated to dryness. Extraction of the crude product with five successive one-liter portions of boiling heptane gave five successive crops of colorless crystals; total wt., 6.4 g. (88% of theoretical); m. p., 87 to 88°. Ten grams was recrystallized from 4 liters of boiling heptane, giving 9.2 g. of colorless crystals; m. p., 80 to 89°. Anal. Calcd. for C<sub>12</sub>H<sub>13</sub>NO<sub>2</sub>: C, 70.90; H, 6.5; N, 6.90. Found: C, 71.12; H, 6.6; N, 6.89.

**6-Hydroxyethoxylepidine Hydrochloride.**—The base was converted to hydrochloride in the usual manner and crystallized from boiling absolute ethanol, giving cream-colored crystals; m. p., 236 to 238°. *Anal.* Calcd. for  $C_{12}H_{13}$ -NO<sub>2</sub>:HCl: N, 5.85; Cl, 14.8. Found: N, 5.49; Cl, 14.2.

General Method for Preparation of 4-(p-Dialkylaminostyryl)-quinoline Derivatives.—A mixture of the lepidine derivative (10 g.) with the *p*-dialkylaminobenzaldehyde (9 molar proportions) and 3.5 g. of granulated, anhydrous zinc chloride was heated under reflux ("drierite" tube) in a bath at 195-200° during six hours (reaction temp.,

<sup>(7)</sup> Tipson, J. Org. Chem., 9, 235 (1944).

 TABLE I

 Melting Points and Analyses<sup>a</sup> of Some 4-Styrylquinoline Derivatives

		Formula								
	M n °C			W N		Mol.		FOULDG		Mol.
4-Styryl-	м. р., с.	Pordiula	C	п	11	w.c.	C	п	14	WL.V
-6-hydroxyquinoline	274 - 275	C17H13NO	82.55	5.3	5.67		82.41	5.3	5.88	
-6-hydroxyethoxyquinoline	138-140	$C_{19}H_{17}NO_2$	78.31	5.9	4.81		78.07	6.2	4.82	
4-(p-Dimethylaminostyryl)-										
-quinoline	139-140°	$C_{19}H_{18}N_2$	83.16	6.6	10.22	274	82.87	6.9	9,98	275
-6-hydroxyquinoline	282 - 283	$C_{19}H_{18}N_2O$	78.58	6.3	9.66		78.67	6.5	10.00	
-6-methoxyquinoline	145 - 146	$C_{20}H_{20}N_{2}O$	78.90	6.6	9.21	304	78.93	6.5	9.37	302
-6-hydroxyethoxyquinoline	170 - 172	$C_{21}H_{22}N_2O_2$	75.41	6.6	8.38		75.05	7.0	8.35	
4-(p-Diethylaminostyryl)-										
-quinoline	120 - 122	$C_{21}H_{22}N_2$	83,39	7.3	9.27	302	83.41	7.6	9.17	300
-6-methoxyquinoline	110 - 112	$C_{22}H_{24}N_2O$	79.47	7.3	8.43	332	79.98	7.1	8.37	324
<sup>a</sup> By Dr. Carl Tiedcke, New Yo	ork, N. Y. $b$	In camphor	(Tiedck	e, Mil	krochemi	e, 18,	223 (19	935)) <b>,</b>	۶ Gilm	an an

Karmas (THIS JOURNAL, 67, 342 (1945)) gave m. p. 141-142°.

180°). It was then allowed to cool to room temperature, shaken with 150 cc. of chloroform plus 100 cc. of 8 N sodium hydroxide solution, and the chloroform solution washed, dried, and evaporated to dryness. Unreacted starting materials were removed by distillation under high vacuum (maximum bath temp., 140°) and the product crystallized.

**4**-(*p*-Dimethylaminostyryl)-quinoline.—The still residue (20.5 g.) was extracted with 82 cc. of boiling absolute ethanol under reflux, cooled to room temperature, and filtered from 0.9 g. of red solid (m. p., above  $260^{\circ}$ ) which contained no chlorine. The filtrate was kept overnight in the refrigerator, giving 8.1 g. of yellowish-brown crystals; m. p.,  $127-130^{\circ}$ . The mother liquor was evaporated to dryness and the material dissolved in 3 volumes of absolute ethanol, yielding a second crop (3.9 g.); total yield of crystals, 12 g. For recrystallization, 10 g. was dissolved in 530 cc. of boiling heptane, the hot solution filtered and cooled, giving 8.8 g. of orange-yellow crystals. We were unable to isolate any 4-(*p*-dimethylaminostyryl)-quinoline when a solution of 10 g. of lepidine and 10.4 g. of *p*-dimethylaminobenzaldehyde in 50 cc. of acetic anhydride was boiled gently under reflux (glascol mantle) during twentyfour hours.

4-(p-Dimethylaminostyryl)-6-methoxyquinoline.—The still residue (18.5 g.) was dissolved in 370 cc. of boiling absolute ethanol under reflux, the solution filtered hot through a fluted filter and diluted with 2777 cc. of water, with spontaneous crystallization. After standing overnight in the refrigerator, a crop of yellow crystals was filtered off and dried; wt., 13.9 g.; m. p., 140°. For recrystallization, 10 g. was dissolved in 200 cc. of boiling absolute ethanol, the hot solution filtered, the filtrate diluted with 100 cc. of water, kept overnight in the refrigerator, and the yellow crystals filtered off and dried; wt., 9.2 g. It is not appreciably affected by 3 N hydrochloric acid during four hours at 100°.

4-(p-Dimethylaminostyryl)-6-hydroxyethoxyquinoline.— The still residue (11.6 g.) was extracted with eight 750-cc. portions of boiling heptane giving 8 successive crops of yellow-orange crystals; wt., 2.7 g.; m. p., 166-168°. For recrystallization, 1.0 g. was dissolved in 2.5 liters of boiling heptane, giving 0.91 g. of yellow-orange crystals.

**4**-(*p*-Diethylaminostyryl)-quinoline.--The still residue (30.0 g.) was dissolved in 150 ec. of absolute ethanol and converted to the dihydrochloride. A total of 11.5 g. of crystalline dihydrochloride was isolated, in three successive erops, from two volumes of absolute ethanol. The dihydrochloride (10 g.) was recrystallized from 30 ec. of boiling absolute ethanol, giving a first crop (5.6 g.) of yellow-tan crystals; m. p., 220-221° (dec.). Anal. Caled. for  $C_{21}H_{22}N_2$ :2HC1: N, 7.47; Cl, 18.9. Found: N, 7.57; Cl, 17.7. Reconversion of 6.2 g. of erystalline dihydrochloride to base gave 5.1 g. of brown, semi-crystalline solid which was extracted with 200 cc. of boiling heptane under reflux, 1.8 g. of gum remaining undissolved. The extract was allowed to cool to room temperature, shaken with charcoal, filtered, and the filtrate kept overnight in the refrigerator, giving a first crop (2.1 g.) of yellow crystals; m. p., 119–121°. Ten grams was recrystallized from 645 cc. of boiling heptane, giving 6.8 g. of yellow crystals.

4-(p-Diethylaminostyryl)-6-methoxyquinoline.—The still residue (25.3 g.) was dissolved in 633 cc. of boiling absolute ethanol, cooled, and kept overnight in the refrigerator. The black solid (2.3 g., m. p. above 265°) was filtered off, the filtrate evaporated to dryness, and the product (23 g.) extracted with 920 cc. of boiling heptane under reflux, 9 g. of gum remaining undissolved. The extract was allowed to cool to room temperature, shaken with charcoal, filtered, and the filtrate kept overnight in the refrigerator, giving 7.7 g. of yellow-orange crystals, m. p., 110-112°. A second crop (2.9 g.) of yellow-orange crystals was isolated. Total yield of crystals was 10.6 g. For recrystallization, 10 g. was dissolved in 400 cc. of boiling heptane, giving 9.2 g. of yellow crystals.

**4-Styryl-6-hydroxyethoxyquinoline.**—Crystalline 6-hydroxyethoxylepidine (5.0 g.) was condensed with freshly distilled benzaldehyde in the presence of anhydrous zinc chloride (reaction temp., 170 to 175°) by the general method. Excess benzaldehyde was distilled off at 20 mm.; the still-residue (9.8 g.) was dissolved in 100 cc. of chloroform, extracted with 50 cc. of 8 N sodium hydroxide, and the chloroform solution washed, dried, filtered, and evaporated to dryness; yield, 9.3 g. of dark-green gum. Extraction of the crude product with one 1-liter portion and two 750-cc. portions of boiling heptane, successively, gave three crops of pale yellow crystal; wt. 1.5 g.; m. p., 133 to 135°. Ten grams was recrystallized from 8 liters of boiling heptane, giving 7.5 g. of pale yellow crystals. Only a 5% yield of crystalline 4-styryl-6-hydroxyethoxy-quinoline was obtained from the hydrolysis of crude 4-styryl-6-benzyloxyethoxyquinoline with 100 volumes of 3 N hydrochloric acid at 100°.

**4-Styryl-6-hydroxyquinoline.**—A solution of recrystallized 4-styryl-6-methoxy-quinoline (5.0 g.) in 200 cc. of 60% sulfuric acid was treated as described for the preparation of 6-hydroxylepidine, giving 4.6 g. of yellow solid; m. p., 248-250° (dec.). For crystallization, 10 g. was dissolved in 1500 cc. of boiling absolute methanol, the hot solution filtered through a fluted filter, and the filtrate diluted with 500 cc. of water, with spontaneous crystallization. After standing overnight in the refrigerator, the yellow crystals were filtered off and dried; `wt. of first crop, 4.1 g.

4-(p-Dimethylaminostyryl)-6-hydroxyquinoline. A solution of recrystallized <math>4-(p-dimethylaminostyryl)-6-meth-oxyquinoline (10.0 g.) in 200 cc. of <math>60% sulfuric acid was

boiled gently under reflux as in the previous experiment. The brown solution was then treated as before except that, owing to the low solubility of the product in alkali, it was found preferable merely to add alkali until neutral, giving 9.1 g. of yellow solid. This crude product was dissolved in 1530 cc. of pyridine at room temperature, filtered, and diluted with 3060 cc. of water with spontaneous crystallization. After standing overnight in the refrigerator, the crystals were filtered off, washed on the filter with three 250-cc. portions of water, and dried; wt., 8.1 g.; m. p., 280-282°. For recrystallization, 10 g. was dissolved in 1,700 cc. of pyridine, filtered, and diluted with 3,400 cc. of water, giving 9.1 g. of yellow crystals.

3,400 cc. of water, giving 9.1 g. of yellow crystals. **2**-(p-Dimethylaminoanilino)-**6**-methoxylepidine.—A mixture of recrystallized 2-chloro-4-methyl-6-methoxyquinoline (10 g.), 6.6 g. of p-dimethylaminoaniline and 25 cc. of glacial acetic acid was boiled gently under reflux ("drierite" tube) for three hours; it was then cooled to room temperature, diluted with 25 cc. of distilled water, and made acid to congo red by dropwise addition of concentrated hydrochloric acid, with spontaneous crystallization. After standing overnight in the refrigerator, he crystals were filtered off and dried; wt., 1.9 g.; m. p., 267 to 268°. Anal. Calcd. for C<sub>11</sub>H<sub>11</sub>NO<sub>2</sub>: N, 7.41. Found: N, 8.07. The analysis and melting point of this material suggest that it is crude 2-hydroxy-4-methyl-6-methoxyquinoline.

The mother liquor was diluted with 100 cc. of water and made alkaline to phenolphthalein (with 70 cc. of 8 N sodium hydroxide) with the separation of semi-crystalline gray solid which was filtered off, washed, and dried; wt., 11.7 g. (79% of theoretical); m. p., 161 to 163°. Teu grams was recrystallized from 200 cc. of absolute ethanol, giving 7.0 g. of gray crystals; m. p., 173 to 174°. Anal. Calcd. for C<sub>19</sub>H<sub>21</sub>N<sub>3</sub>O: C, 74.22; H, 6.89; N, 13.68. Found: C, 74.00; H, 6.64; N, 13.62. **2**-(p-Diethylaminoanilino)-6-methoxylepidine.—A mix-

2-(p-Diethylaminoanilino)-6-methoxylepidine.—A mixture of recrystallized 2-chloro-4-methyl-6-methoxyquinoline (10 g.) and 7.9 g. of *p*-diethylaminoaniline was dissolved in 25 cc. of glacial acetic acid and treated as in the previous experiment. After adding water (only) and standing overnight in the refrigerator, the crystals were filtered off, washed, and dried; wt., 4.4 g.; m. p., 269 to 270°. It was recrystallized from 120 volumes of absolute ethanol, giving 3.4 g. of colorless crystals; m. p., 269 to 270°. Anal. Calcd. for C<sub>11</sub>H<sub>11</sub>NO<sub>2</sub>: C, 69.80; H, 5.86; N, 7.41.• Found: C, 69.60; H, 5.39; N, 8.02. The analysis and melting point of this material indicate that it is probably 2-hydroxy-4-methyl-6-methoxyquinoline.

Addition of hydrochloric acid to the acetic acid mother liquor gave no crystals; it was therefore treated as in the previous experiment, with the separation of a dark gum which was dissolved in 100 cc. of chloroform, washed, dried, and evaporated to dryness, giving a dark-green, semicrystalline base. Gray, crystalline product (4.8 g.) was isolated in two successive crops from 20 volumes of absolute ethanol; m. p., 133 to 135°. Ten grams was recrystallized from 200 cc. of absolute ethanol giving 8.5 g. of gray crystals; m. p., 133-135°. *Anal.* Calcd. for  $C_{21}H_{25}N_3O$ : C, 75.17; H, 7.5; N, 12.54. Found: C, 74.83; H, 7.6; N, 12.22.

Action of p-Acetylaminobenzenesulfonyl Chloride on 2-Hydroxy-6-methoxylepidine.—Dry, recrystallized 2-hydroxy-6-methoxylepidine (10 g.) was suspended in 200 cc. of dry pyridine, 13.6 g. of p-acetylaminobenzenesulfonyl chloride was added and the flask tightly stoppered. After standing at room temperature during four days, 2 g. of undissolved material was filtered off, the filtrate cooled to  $-10^{\circ}$  in ice-salt, and 20 cc. of water added in small portions with swirling, the temperature being kept below  $-5^{\circ}$ ; 225 cc. of water was then added, giving 13.8 g. of colorless crystals; m. p., 167-168°. It was recrystallized from 33 volumes of boiling absolute ethanol, or 20 volumes of boiling acetone, giving iridescent, colorless platelets; m. p., 167°. Anal. Calcd. for C<sub>19</sub>H<sub>18</sub>N<sub>2</sub>O<sub>5</sub>S: C, 59.03; H, 4.7; N, 7.25; S, 8.30; Cl, 0.00. Found: C, 59.03; H, 4.8; N, 7.01; S, 8.09; Cl, 0.00.

## Summary

1. 6-Benzyloxyethyloxylepidine has been prepared; hydrolysis gave an 88% yield of crystalline 6-hydroxyethoxylepidine.

2. Satisfactory procedures for the preparation of 4-styrylquinoline derivatives are given. The properties of the 4-(p-dimethylaminostyryl) and 4-(p-diethylaminostyryl) derivatives of quinoline and 6-methoxyquinoline, and of the 4-styryl and 4-(p-dimethylaminostyryl) derivatives of 6-hydroxyethoxyquinoline, are given.

3. 4-Styryl- and 4-(p-dimethylaminostyryl)-6methoxyquinoline are not appreciably affected by 3 N hydrochloric acid during four hours at 100°; demethylation (at position 6) of the 4styryl- and 4-(p-dimethylaminostyryl-6-methoxyquinolines, by means of 60% sulfuric acid, is reported.

4. The preparation of two 2-(p-dialkylaminophenyl)-amino-6-methoxylepidine derivatives is described.

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