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Studies in the Quinoline Series. I. Some 2-(*p*-Dialkylaminostyryl)-quinoline Derivatives[1]

BY R. STUART TIPSON

Although the chemotherapeutic properties of a large number of substituted 2-styryl-quinolinium salts have been rather intensively studied,[2] very little attention appears to have been paid to the 2-(*p*-dialkylaminostyryl)-quinoline bases. It seemed of interest to prepare a number of these substances for chemotherapeutic evaluation but a search of the literature revealed that, although several of them have been reported, the descriptions of the experimental procedures employed are meager and the yields of product have not been recorded.

In order to find a method suitable for the preparation of these compounds in quantity, a number of the procedures which have been used for the synthesis of various styrylquinolines have now been applied to the preparation of the known 2-(*p*-dimethylaminostyryl)-quinoline, and the respective yields ascertained. These methods include heating molar proportions of the reactants alone, or with acetic anhydride,[3] hydrochloric acid,[4] or zinc chloride.[5] The conditions chosen usually resembled, as closely as possible, those of the earlier workers; the details are given in the experimental section. The use of acetic anhydride gave an inferior yield (13%); with hydrochloric acid or zinc chloride the yield was satisfactory (51 and 68%, respectively), but removal of these substances was necessary at the end of the reaction. Furthermore, with zinc chloride, a small amount of *p*-dimethylaminobenzylidene diquinaldine was also formed.

We were unable to isolate any product after heating molar proportions of the reactants alone at 150° during forty-five minutes (the conditions presumably employed by Noelting and Witte[6]), and the yield amounted to only 2.5% of the theoretical under Brahmachari's conditions[7] (fifteen minutes at the boiling point, about 255°). However, because of its speed and the ease of isolation of product, we have studied Brahmachari's method in some detail and have been able to adapt it to the preparation of this and similar compounds in good yield. The reactants were heated under reflux (Stark and Dean trap) in a bath at 275°; when the reaction was interrupted from time to time, the reaction products removed, and the unchanged reactants again heated, it was found that the total yield could be raised to as high as 86% of the theoretical.

For a standard procedure for the preparation of 2-(*p*-dialkylaminostyryl)-quinoline derivatives, we therefore chose to use two treatments at 275° (bath temp.), each of two hours duration; unreacted starting-materials were removed after each treatment, by means of solvents or by distillation under high vacuum. Some of the properties of these substances are recorded in Table I, from which it may be seen that changing the side-chain alkyl groups from methyl to ethyl increases the solubility and invariably lowers the melting point; it also renders the compounds more difficult to isolate in crystalline form. Substitution of a methyl group at position 6 decreases the solubility and raises the melting point; substitu-

(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) Browning, *et al.*, *Brit. Med. J.*, II, 326 (1923); *Proc. Roy. Soc.* (London), **B105**, 99 (1929); Parkin, *Onderstepoort J. Vet. Sci.*, **4**, 287 (1935); Browning and Gulbransen, *J. Pharmacol.*, **57**, 56 (1936).

(3) Bennett and Pratt, *J. Chem. Soc.*, 1465 (1929); Mathur and Robinson, *ibid.*, 1520 (1934).

(4) (a) Pfeiffer *et al.*, *Ann.*, **441**, 265 (1925); (b) Rupe, *et al.*, *Helv. Chim. Acta*, **18**, 1395 (1935).

(5) Jacobsen and Reimer, *Ber.*, **16**, 1082, 2602 (1883); Porai-Koschitz, *Z. Farben-Ind.*, **6**, 291 (1907).

(6) Noelting and Witte, *Ber.*, **39**, 2749 (1906).

(7) Brahmachari, *et al.*, *J. Indian Chem. Soc.*, **7**, 527 (1930).

TABLE I

YIELDS, MELTING POINTS, AND ANALYSES[a] OF SOME 2-(*p*-DIALKYLAMINOSTYRYL)-QUINOLINES

	Total yield, %[b]	Yield of crystals, %[b]	Vol. (in cc.) of absolute ethanol (E) plus chloroform (C) for recryst. of 10 g.	M. p., °C.	Formula	Analyses, % Calculated C	H	N	Mol. wt.	Found C	H	N	Mol. wt.[c]
2-(*p*-Dimethylaminostyryl)-													
-quinoline		63[d]	100E + 50C	184–185[e]	$C_{19}H_{18}N_2$	83.16	6.6	10.22	274	83.23	6.2	10.52	273
-4-methylquinoline	90[f]	61	50E	139–141	$C_{20}H_{20}N_2$	83.28	7.0	9.72	288	83.27	6.7	9.93	290
-6-methylquinoline	98.5[d]	56.5	75E + 50C	195–197[g]	$C_{20}H_{20}N_2$	83.28	7.0	9.72	288	83.23	7.0	9.95	286
-4,6-dimethylquinoline	87[d,f,h]	51	100E	162–163	$C_{21}H_{22}N_2$	83.39	7.3	9.27	302	83.68	7.3	9.05	300
-4-methyl-6-ethoxyquinoline	96[d,f]	59	100E + 30C	173–174	$C_{22}H_{24}N_2O$	79.47	7.3	8.43	332	79.47	7.5	8.63	329
-4-phenylquinoline	97[d,f,h]	82	100E + 30C	167–168	$C_{24}H_{22}N_2$	85.67	6.3	8.00	350	85.64	6.0	8.11	351
2-(*p*-Diethylaminostyryl)-													
-quinoline	86.5[f]	63	30E	101–103	$C_{21}H_{22}N_2$	83.39	7.3	9.27	302	83.63	6.9	9.65	305
-4-methylquinoline	93[f]	46[i]		85–87	$C_{22}H_{24}N_2$	83.49	7.65	8.86	316	83.56	7.48	8.84	309
-6-methylquinoline	92[d,f]	71.5	100E + 10C	135–136	$C_{22}H_{24}N_2$	83.49	7.65	8.86	316	83.57	7.33	8.98	314
4,6-dimethylquinoline	91[f,h]	66	100E	151–153	$C_{23}H_{26}N_2$	83.58	7.9	8.48	330	83.70	8.1	8.59	334
-4-methyl-6-ethoxyquinoline	71[f]	41	100E + 10C	143–144	$C_{24}H_{28}N_2O$	79.95	7.8	7.78	360	79.63	7.7	7.94	359
-4-phenylquinoline	80[f,h,j]	46[j,k]	100E + 10C	135–136	$C_{27}H_{26}N_2$	85.67	6.9	7.41	378	85.24	6.9	7.42	377

[a] By Dr. Carl Tiedcke, New York, N. Y. [b] Of theoretical, calculated as mono-(dialkylaminostyryl) derivative. [c] In camphor (Tiedcke, *Mikrochemie*, **18**, 223 (1935)). [d] Unchanged reactants removed with absolute ethanol. [e] Noelting and Witte (*Ber.*, **39**, 2749 (1906)) gave m. p., 177°; Pfeiffer, *et al.* (*Ann.*, **441**, 265 (1925)), m. p. 179°; Brahmachari, *et al.* (*J. Indian Chem. Soc.*, **7**, 527 (1930)), m. p. 175°; Rupe, *et al.* (*Helv.*, **18**, 1395 (1935)), m. p., 183.5–184.5°. [f] Unchanged reactants removed by distillation at 0.1 mm. [g] Porai-Koschitz gave m. p. 198°; Brahmachari, *et al.*, m. p. 199°. [h] 4,6-Dimethyl- and 4-phenyl-quinaldine were kindly presented by the Carbide and Carbon Chemicals Corporation. [i] After purification through the dihydrochloride. [j] Single treatment at 275°. [k] After purification through the monohydrochloride.

tion of a methyl group at position 4 increases the solubility and lowers the melting point.

The yields given in column 3 of Table I are yields of crystalline product isolated; in certain cases this was considerably less than the total yield (column 2) of reaction product. This may be ascribed to concomitant formation of one or more of the following substances: the intermediate carbinol derivative, the *p*-dialkylaminobenzylidene diquinaldine derivative, the geometrical isomer or the dimer of the monostyryl compound; and, in the case of the products from 2,4-dimethylquinoline and its derivatives, the corresponding 2,4-di-(*p*-dialkylaminostyryl) compounds. In no case could the by-product(s) be isolated in crystalline form but the *crystalline* substances had molecular weights agreeing closely with those calculated for *mono*-(*p*-dialkylaminostyryl)-quinoline derivatives. Since Fischer[8] has shown that the methyl group at position 2 reacts more readily with aldehydes than that at position 4, it is assumed that the compounds prepared from 2,4-dimethylquinoline and its derivatives have the *p*-dialkylaminostyryl group at position 2.

It appears that certain of the earlier workers failed to realize that, in these condensations, more than one product may result. It is now found, as previously mentioned, that treatment of 1 mole of quinaldine with 1 mole of *p*-dimethylaminobenzaldehyde in the presence of 1 mole of anhydrous zinc chloride during two hours at 145° (bath temp.) gives rise to a 68% yield of the corresponding styrylquinoline together with a small amount of *p*-dimethylaminobenzylidene diquinaldine. On the other hand, treatment of 2 moles of quinaldine with 1 mole of the aldehyde in the presence of 0.5 mole of zinc chloride during three hours at 160° (bath temp.) gives more of the diquinaldine derivative than of the styryl derivative. These two compounds can be distinguished by melting point and molecular weight determinations, but elementary analysis is not sufficiently precise; this may explain the discrepancies in the value reported for the melting point of this styryl compound by earlier workers (see Table I).

It should be mentioned that 2-(*p*-dimethylaminostyryl)-quinoline is unaffected by cold, concentrated hydrochloric acid (during fifty-five days at room temperature) or by hot 3 *N* hydrochloric acid (during four hours at 100°). Occasion was also taken to ascertain the respective yields of the two monomethiodides formed on treatment with methyl iodide in a sealed tube at 100°; it was found that the dimethiodide is formed simultaneously.

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

Experimental

Apparatus with ground glass joints was employed in al the preparative work.

***p*-Dimethylaminobenzylidene Diquinaldine.**—A mixture of quinaldine (40 g.) with 20.8 g. of *p*-dimethylaminobenzaldehyde and 9.5 g. of granulated, anhydrous zinc chloride was heated under reflux with mechanical stirring (mercury seal) in a bath at 160° during three hours; the reaction temperature rose to 153° and then slowly fell to 135°. On cooling, the mixture set to a purple, almost solid mass which was extracted with two 100-cc. and two 50-cc. portions of cold chloroform (by stirring, and decanting the extract). It was then filtered with suction and the insoluble purple crystals were dried; wt., 26 g.

The chloroform filtrate and washings were united, and

shaken with 25 cc. of 8 *N* sodium hydroxide solution; the chloroform layer was washed with water, dried with anhydrous sodium sulfate, filtered, and the filtrate evaporated to dryness, giving 41 g. of a pale yellow, crystalline mass which was dissolved in 2 volumes of boiling absolute ethanol under reflux. On cooling, 25.5 g. of pale lemon-yellow crystals was deposited (filtrate, "A"); m. p., 133–136°. The crystals (25.5 g.) were dissolved in 255 cc. of boiling absolute ethanol, the hot solution filtered, and the filtrate kept overnight in the refrigerator, giving 23 g. of pale yellow crystals; m. p. 138–139°. The substance (10 g.) is readily and completely soluble in a mixture of 50 cc. of chloroform with 100 cc. of absolute ethanol at room temperature, and does not crystallize from this solution on standing overnight in the refrigerator.

Anal. Calcd. for $C_{29}H_{27}N_3$: C, 83.41; H, 6.5; N, 10.07; mol. wt., 417. Found: C, 83.24; H, 6.1; N, 9.74; mol. wt., 400.

This material therefore consisted essentially of *p*-dimethylaminobenzylidene diquinaldine, but it still contained a trace of the *p*-dimethylaminostyryl derivative. It was purified as follows: 10 g. was suspended in 100 cc. of absolute ethanol, 7 cc. of concentrated hydrochloric acid was added, and the purple solution evaporated to dryness. The product was shaken with 100 cc. of water and a trace of insoluble purple crystals filtered off (monohydrochloride of the styryl derivative). Charcoal was added to the purple filtrate, the suspension boiled and filtered, giving a colorless filtrate which was evaporated to dryness and the product crystallized from absolute ethanol (in colorless crystals).

Anal. Calcd. for $C_{29}H_{27}N_3 \cdot 3HCl$: N, 7.98; Cl, 20.20. Found: N, 7.76; Cl, 20.10.

This colorless trihydrochloride was reconverted to the base, which consisted of colorless crystals; m. p. 150°; mol. wt. found, 411.

Filtrate A was evaporated to dryness, yielding 15.5 g. of a brown, mobile liquid which was distilled at 0.05 mm. The distillate (11 g.) had $n^{20}D$ 1.6115 and consisted solely of quinaldine ($n^{20}D$ 1.6115); the still residue (4 g.) was a brown glass which was dissolved in 40 cc. of boiling absolute ethanol and cooled, yielding 1 g. of crude crystals (styryl derivative); m. p. 173–175°.

The purple crystals (26 g.) were suspended in 100 cc. of water, sodium carbonate (26 g.) was added and the suspension boiled on a wire gauze under reflux during fifteen minutes, the color of the suspension gradually changing from purple to yellow. The suspension was now cooled and shaken vigorously with 200 cc. of chloroform and 150 cc. of 8 *N* sodium hydroxide solution; all of the material dissolved, in one layer or the other. The chloroform solution was washed with water, dried with anhydrous sodium sulfate, and evaporated to dryness, giving 17.3 g. of golden-yellow crystals; m. p. 184–185°. This material (17.3 g.) was recrystallized from 86.5 cc. of chloroform plus 173 cc. of absolute ethanol, yielding 12.8 g. of crystals (styryl derivative); m. p. 184–185°.

Anal. Calcd. for $C_{19}H_{18}N_2$: C, 83.16; H, 6.6; N, 10.22; mol. wt., 274. Found: C, 83.33; H, 6.9; N, 10.20; mol. wt., 267.

2-(*p*-Dimethylaminostyryl)-quinoline.—In each experiment a mixture of 20 g. of quinaldine with 21 g. of *p*-dimethylaminobenzaldehyde was used.

(a) **In Presence of Zinc Chloride.**[5]—Anhydrous zinc chloride (19.1 g.) was added to the mixture which was then heated, without stirring, under reflux at 133° (bath temp., 140–145°) during two hours. The purple, crystalline mass was shaken with 200 cc. of chloroform, the suspension filtered, and the insoluble, purple crystals washed with 100 cc. of chloroform and dried. The purple crystals (29.3 g.) were treated as described in the preceding experiment, giving 10 g. of yellow crystals; m. p. 184–185°.

The chloroform filtrate and washings were united, shaken with 8 *N* sodium hydroxide (50 cc.) and the product isolated as described in the preceding experiment, yielding a crystalline mass (32 g.); treatment with 105 cc. of absolute ethanol gave 16.1 g. of yellow crystals; m. p. 183–184°; total yield, 26.1 g. (68%).

The mother liquor was evaporated to dryness, giving a brown sirup which was dissolved in 50 cc. of absolute ethanol and kept overnight at room temperature. The very pale yellow crystals which had separated were filtered off, washed with two 25-cc. portions of heptane and two 25-cc. portions of absolute ethanol, and dried. This material weighed 2 g.; m. p. 140–142°.

Anal. Calcd. for $C_{29}H_{27}N_3$: C, 83.41; H, 6.5; N, 10.07; mol. wt., 417. Found: C, 83.05; H, 6.4; N, 9.95; mol. wt., 390.

The mother liquor was evaporated to dryness and the material distilled at 0.05 mm., leaving 3.7 g. of still-residue. This was crystallized from 37 cc. of absolute ethanol, giving 2.5 g. of crude crystals, m. p. 136–138°.

(b) **In Presence of Concentrated Hydrochloric Acid.**[4]—The mixture was dissolved in absolute ethanol (105 cc.), concentrated hydrochloric acid (12 cc.) was added, the resulting dark-red solution was evaporated to dryness, and the crystalline mass heated under diminished pressure (13 mm.), in a bath at 150°, during two hours; water collected in the receiver. The black crystalline product was shaken with chloroform plus 8 *N* sodium hydroxide solution (50 cc.), the chloroform solution dried and evaporated to dryness. The crystalline product was stirred with absolute ethanol (50 cc.), filtered, and washed with heptane (2 × 25 cc.) and ethanol (2 × 25 cc.); wt., 17 g.; m. p., 183–184°; mol. wt. found, 272. The mother liquor was evaporated to dryness (23 g.) and distilled at 0.05 mm., leaving 2.5 g. of crystalline still-residue which was recrystallized from absolute ethanol; m. p., 182–184°; mol. wt. found, 274; total yield, 19.5 g. (51%).

(c) **In Presence of Acetic Anhydride.**[4]—Acetic anhydride (26 cc.) was added to the mixture which was then boiled under reflux at 150–159° (bath temp., 175°) during two hours. It was cooled, mixed with water (250 cc.) and shaken with chloroform plus sodium hydroxide solution. The chloroform solution was dried and the product isolated as in (b), giving 5 g. (13%) of yellow crystals; m. p. 181–183°. The mother liquor was evaporated to dryness and distilled at high vacuum, giving 10 g. of dark red, glassy still residue from which 2 g. of crystals (m. p., 140°) was isolated on treatment with 50 cc. of absolute ethanol.

(d) **Alone, or in Presence of "Drierite."**—When the mixture was heated under reflux in a bath at 150°, either alone during forty-five minutes,[6] or in the presence of drierite (20 g.) during two hours, no reaction product could be isolated by treatment with absolute ethanol.

(e) **Modification of Brahmachari's Method.**[7]—The mixture was boiled in a two-necked flask (into one neck of which a thermometer was inserted), under reflux condenser (Stark and Dean trap), in a bath at 275°, for the stated period of time. The temperature of the boiling mixture slowly rose from 254 to 270°, and water collected in the trap. It was then allowed to cool to room temperature, the crystalline mass stirred with absolute ethanol (50 cc.) and filtered. The golden-yellow crystals were washed with heptane (10 cc.) and absolute ethanol (10 cc.) and dried; m. p. (crude), 175–181°.

When the condensation was performed for various periods of time the yields were as follows: 2.5% (0.25 hour); 28% (1 hour); 39% (2 hours); 44% (4.5 hours). Hence the reaction tended to reach an equilibrium condition, presumably because the water formed during the reaction had not been removed efficiently. However, when the reaction was interrupted from time to time, the reaction product and water removed, and the unchanged reactants again heated the total yields were as follows: 53% (1 + 1 hours); 70% (1 + 1 + 1 hours); 86% (1 + 1 + 1 + 2 hours); 59.5% (4.5 + 1 hours); 72.5% (4.5 + 1 + 1 hours); 86% (4.5 + 1 + 1 + 1 hours). For a standard procedure we therefore chose to use two treatments, each of two hours duration.

Recrystallization of the product from boiling absolute ethanol[4,6,7] is impracticable since over 70 volumes of boiling solvent are necessary; recrystallization from benzene[6]

is inadvisable since the compound is more soluble than unchanged aldehyde in cold benzene.

Action of Methyl Iodide on 2-(*p*-Dimethylaminostyryl)-quinoline.—The dry, recrystallized base (10 g.) was treated with 30 cc. of methyl iodide[4b] plus 40 cc. of absolute methanol in a sealed tube at 100° during five hours. On cooling to room temperature, the reaction mixture consisted of a fairly solid mass of large red crystals suspended in red solution. The solid was filtered off and dried, giving a crop of chocolate-brown crystals; wt., 19.5 g. The filtrate was evaporated to dryness, yielding 2.5 g. of yellow-orange crystals.

The material was now extracted with 100 volumes of boiling water and the hot suspension filtered. The insoluble, dark purple residue (wt., 1.5 g.) consisted of 2-(*p*-dimethylaminostyryl)-quinolinium methiodide.

The purple, aqueous filtrate was again heated to boiling, charcoal was added, and the hot suspension filtered, giving a colorless filtrate which, on cooling, deposited long, colorless needles of β-2-quinolylstyryltrimethylammonium iodide (8.5 g.).

Anal. Calcd. for $C_{20}H_{21}N_2I$: C, 57.68; H, 5.1; N, 6.73; I, 30.50. Found: C, 57.98; H, 5.0; N, 6.85; I, 30.53.

The mother liquor was evaporated to dryness, giving a light yellow crystalline mass (8.5 g.) which gradually darkened to a brown color on keeping. It was quite soluble in water and had a composition agreeing with that calculated for the dimethiodide.

Anal. Calcd. for $C_{21}H_{24}N_2I_2$: I, 45.49. Found: I, 43.76.

Although Rupe, *et al.*,[4b] have prepared the two monomethiodides, they do not record the formation of this dimethiodide. They do, however, mention that they accomplished recrystallization of the trimethylammonium compound from water with considerable loss.

An excellent preliminary separation of the purple methiodide may be achieved by extraction in a Soxhlet apparatus with acetone (in which the colorless methiodides are much less soluble).

The colorless monomethiodide was converted to its monohydrochloride by suspending 5 g. of the base in 200 cc. of 50% aqueous ethanol and adding concentrated hydrochloric acid dropwise until the solution was slightly acid to congo red. The solution was evaporated to dryness under diminished pressure, with occasional addition of absolute ethanol. The product (5.4 g.) was stirred with 100 cc. of absolute ethanol and filtered, yielding 4.2 g. of yellow crystals.

Anal. Calcd. for $C_{20}H_{21}N_2I \cdot HCl$: Cl, 7.84; I, 28.05. Found: Cl, 8.00; I, 30.40.

Action of Hydrochloric Acid on 2-(*p*-Dimethylaminostyryl)-quinoline: (a) Cold, Concentrated Acid.—2-(*p*-Dimethylaminostyryl)-quinoline (10 g.) was dissolved in 25 cc. of cold, concentrated hydrochloric acid, the flask tightly stoppered and kept at room temperature for fifty-five days. The light purple solution was now evaporated to dryness, the resulting pale yellow crystals suspended in 100 cc. of water, the purple mixture treated with 50 cc. of 8 *N* sodium hydroxide and the orange-yellow precipitate extracted with 800 cc. of benzene.

The benzene solution was washed with water, dried, and evaporated to dryness, yielding 10 g. of yellow crystals; m. p., 184–185°.

Anal. Calcd. for $C_{19}H_{18}N_2$: N, 10.22; Cl, 0.00. Found: N, 10.30; Cl, 0.00.

(b) **Hot 3 N Acid.**—2-(*p*-Dimethylaminostyryl)-quinoline (10 g.) was converted to the monohydrochloride (described later), which was dissolved in 100 cc. of 3 *N* hydrochloric acid. This solution was heated under reflux in a boiling water-bath during four hours, and the product isolated as in (a), giving 10 g. of yellow crystals; m. p. 184–185°. It was recrystallized from 5 volumes of chloroform plus 10 volumes of absolute ethanol, yielding 7.5 g. of yellow crystals; m. p., 184–185°.

General Method for Preparation of 2-(*p*-Dialkylaminostyryl)-quinoline Derivatives.—A mixture of the quinaldine derivative (20 g.) with the *p*-dialkylaminobenzaldehyde (1 molar proportion) was heated as described under (e), in a bath at 275° during two hours. The mixture was then allowed to cool to room temperature and unreacted starting materials were removed by distillation under high vacuum or, in a few cases, by means of absolute ethanol. The mixture of unreacted materials was then reheated at 275° during two hours, as before, and the product isolated in the same manner.

4-Phenylquinaldine boils at 112° at 0.05 mm. pressure (bath temp., 130–132°); it solidifies in the receiver to colorless crystals having m. p. 98–99°. It may also be purified from 7.5 volumes of boiling dry ether but half of the material remains in the mother liquor.)

Recrystallization of Bases.—All the bases were much more soluble in chloroform than in ethanol. Each compound (10 g.) was dissolved in the stated volume (Table I) of boiling solvent(s) under reflux; the hot solution was filtered through a fluted filter, cooled, and kept overnight at room temperature. All the bases were obtained as yellow crystals. **2-(*p*-Diethylaminostyryl)-4-methylquinoline** (10 g.) was recrystallized from 200 cc. of heptane.

Hydrochlorides.—In order to obtain the 2-(*p*-diethylaminostyryl) derivatives of 4-methyl- and 4-phenylquinoline in crystalline form it was necessary first to transform them to the hydrochlorides.

2-(*p*-Diethylaminostyryl)-4-methylquinoline Dihydrochloride.—A sample of still residue (14.5 g.) was dissolved in 100 cc. of absolute ethanol, and concentrated hydrochloric acid was added until the solution was acid to congo red. The purple solution was evaporated to dryness, giving a yellow crystalline mass (18 g.) which was treated with 100 cc. of absolute ethanol and filtered, yielding 9.5 g. of light yellow crystals having a greenish tinge. The mother liquor yielded a further 2.5 g. of crystals on evaporating to dryness and dissolving in 50 cc. of absolute ethanol.

Anal. Calcd. for $C_{22}H_{24}N_2 \cdot 2HCl$: N, 7.2; Cl, 18.2. Found: N, 6.8; Cl, 17.7.

The dihydrochloride was reconverted to base in the usual manner and then crystallized.

2-(*p*-Diethylaminostyryl)-4-phenylquinoline Monohydrochloride.—The still residue could not be obtained crystalline; it was converted to the dihydrochloride, which also could not be crystallized. It was therefore converted to the monohydrochloride, approximately as previously described[9] for 6′-(β-chloroethyl)-apocupreine.

The crude dihydrochloride (33.5 g.) was shaken with 100 cc. of water plus 100 cc. of chloroform. The chloroform layer became rich purple colored, and the aqueous layer was pinkish-red and acid to congo red. The aqueous layer was evaporated to dryness, giving 1.5 g. of a brown flaky glass which was insoluble in chloroform. The chloroform layer was evaporated to dryness, yielding 31.5 g. of a purple, partly crystalline mass which was treated with 64 cc. of absolute ethanol and kept overnight at room temperature. The purplish-black crystals were filtered off and dried; wt., 16.5 g.

Anal. Calcd. for $C_{27}H_{26}N_2 \cdot HCl$: N, 6.76; Cl, 8.55. Found: N, 6.46; Cl, 8.33.

A further 1.5 g. of crystals was obtained by evaporating the mother liquor to dryness and treating with 30 cc. of absolute ethanol.

The *crystalline* hydrochloride (18 g.) was reconverted to free base, giving 16.5 g. of a brown glass which was crystallized by adding 33 cc. of absolute ethanol.

2-(*p*-Dimethylaminostyryl)-quinoline monohydrochloride is best prepared from the easily hydrolyzed dihydrochloride. Concentrated hydrochloric acid (7 cc.) was added to a suspension of 10 g. of the base in 200 cc. of methanol plus 100 cc. of ethanol. The resulting purple solution was evaporated to dryness, giving a quantitative yield of colorless crystals of the dihydrochloride.

Anal. Calcd. for $C_{19}H_{18}N_2 \cdot 2HCl$: N, 8.07; Cl, 20.43. Found: N, 7.47; Cl, 19.61.

(9) Tipson and Cretcher, THIS JOURNAL, **64**, 1162 (1942).

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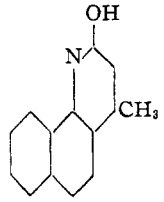
[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

Derivatives of Benzo(h)quinoline

BY RICHARD J. GOBEIL[1] AND CLIFF S. HAMILTON

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).