[CONTRIBUTION FROM THE DEPARTMENT OF RESEARCH IN PURE CHEMISTRY, MELLON INSTITUTE OF INDUSTRIAL RESEARCH]

Studies in the Quinoline Series. II. The Monoaminophenylquinaldylcarbinols

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Before embarking on a study of some of the lepidyl carbinols, we decided to attempt a clarification of the confusing data in the literature concerning certain quinaldyl carbinols. According to Wartanian,[1] quinaldine reacts with *m*-nitrobenzaldehyde in the presence of zinc chloride (about four hours at 100°) to give a mixture of the carbinol and the corresponding styryl derivative but Taylor and Woodhouse[2] asserted that "the observations of Wartanian . . . are incorrect."

We now find that the *o*-, *m*- and *p*-nitrophenylquinaldylcarbinols may all be prepared with great ease by the method of Bulach[3] (in the following yields: *p*-, 75; *o*-, 69; and *m*-, 44% of the theoretical) provided that there is no trace of mineral acid present during the condensation. If the reaction mixture contains even a trace of acid, the resulting product is the corresponding styryl derivative or a mixture of this with the carbinol.

The literature reports only a single melting point each for the *o*- and *p*-nitro carbinol derivatives; we find that all three substances exhibit two melting points, depending on whether heated rapidly or slowly. On cooling until crystallized and remelting, the melting point is greatly lowered in each case. This may be attributed to the fact that heat alone will convert these carbinols to the corresponding styryl derivatives; of the three, the *p*- appears to be the least stable to heat.

As a confirmation of structure we have prepared the acetate of α-(*m*-nitrophenyl)-β-(2-quinolyl)-ethanol; attempts to prepare the corresponding benzoyl and tosyl esters led to the formation of 2-(*m*-nitrostyryl)-quinoline. Bromination of the *m*-nitro carbinol, using conditions under which the nitrostyryl compounds give the dibromonitrostyryl derivatives, resulted in a mixture of unchanged starting material with bromoderivatives.

The three 2-(mononitrostyryl)-quinolines were prepared in quantitative yield by treating the corresponding carbinol with boiling acetic anhydride.[1] They could also be isolated (in 88% yield) by acidifying, before heating, the same mixtures used for preparing the carbinols. The melting points and solubilities found for the three nitrostyryl compounds were not in agreement with most of the data on record.

In conformity with the experience of other workers, the reduction methods of Bulach[4] and West[5] were found to be inapplicable to the reduction of these nitro carbinols to the amino carbinols, owing to transformation to the styryl derivatives in the presence of mineral acid. However, we have succeeded in preparing the amino carbinols in about 50% yield by catalytic reduction with hydrogen.

(1) Wartanian, *Ber.*, **23**, 3644 (1890).
(2) Taylor and Woodhouse, *J. Chem. Soc.*, **129**, 2971 (1926).
(3) Bulach, *Ber.*, **20**, 2046 (1887).
(4) Bulach, *ibid.*, **22**, 285 (1889).
(5) West, *J. Chem. Soc.*, **127**, 494 (1925).

Experimental

***p*-Nitrobenzaldiacetate** was prepared as described in "Organic Syntheses"[6] but the average yield of product was 55% of the theoretical.

***o*-Nitrobenzaldiacetate** was prepared in the same manner but the yield was found to depend on the length of time the reaction was permitted to proceed after adding the chromium trioxide, as follows: 8.0% (ten minutes); 21.2% (five hours); 15.8% (seven hours). For a standard procedure we therefore chose five hours as the reaction time[7]; furthermore, a second crop was isolated in the following manner. The aqueous mother liquor of the first crop was extracted with chloroform, the extract washed with sodium bicarbonate solution, dried with anhydrous sodium sulfate, and evaporated to dryness; the resulting brown sirup was treated with 5.3 volumes of heptane and kept overnight in the refrigerator whereupon crystals separated. Using Thiele and Winter's proportions[7] of reactants (reaction time, five hours) the total yield amounted to only 12% of the theoretical.

***p*-Nitrobenzaldehyde.**—By a slight modification of the method in "Organic Syntheses"[6] the yield was increased; the aqueous alcohol mother liquor of the second crop was extracted with chloroform, the chloroform extract washed and dried as above, and evaporated to dryness; total yield, almost quantitative. It was recrystallized by dissolving in 5 volumes of boiling chloroform, filtering the hot solution, adding 10 volumes of cold heptane to the cold filtrate, and keeping overnight in the refrigerator. The crystals were dried in the vacuum oven at 80°.

***o*-Nitrobenzaldehyde.**—Hydrolysis of the crystalline diacetate was performed as in "Organic Syntheses"[6] but, after refluxing and filtering, only an oil appeared. Water (9.3 volumes, calculated on the original diacetate) was added and the mixture kept overnight in the refrigerator, giving a crop of crystals. The mother liquor was extracted with chloroform and the extract washed, dried and evaporated to dryness as above. Heptane (7.5 volumes) was added, giving a second crop of crystals; total yield, 83%. It was recrystallized from 4 volumes of chloroform plus 12 volumes of heptane in the same manner as for the *p*-aldehyde.

General Method for Preparation of Nitrophenylquinaldylcarbinols.—The nitrobenzaldehyde (10.6 g., completely free from acid[8]) was treated[3] with quinaldine (10 g.) at 120° (temperature of reaction mixture) during three hours. The mixture was then cooled to room temperature, treated with 50 cc. of ethanol and kept overnight in the refrigerator. The crystals were filtered off, washed with two 10-cc. portions of ethanol, and dried in the vacuum desiccator over phosphorus pentoxide. The crude product was then recrystallized from a boiling mixture of ethanol and chloroform (Table I); the hot solution was filtered and the cooled filtrate kept overnight in the refrigerator. The *o*- and *m*-carbinols were obtained as colorless crystals, the *p*-derivative as pale yellow crystals.

(6) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 441.
(7) Thiele and Winter, *Ann.*, **311**, 353 (1900); "Organic Syntheses," Vol. 24, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 75.
(8) The commercial aldehydes often contain mineral acid.

TABLE I

MELTING POINTS AND ANALYSES[a] OF THE NITRO- AND AMINOPHENYLQUINALDYLCARBINOLS AND THE 2-(NITROSTYRYL)-QUINOLINES

-phenyl quinaldyl carbinol	Vol. (cc.) of absolute ethanol (E) plus chloroform (C) for recryst. of 10 g.	M. p., °C. Initial fast	Initial slow	Second (cooled and reheated)	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
o-Nitro	100E + 133C	167–168[b]	162–163	158–160	$C_{17}H_{14}O_3N_2$	69.36	4.8	9.53	69.17	5.1	9.76
m-Nitro	100E + 85C	156–157	153–154	116–117	$C_{17}H_{14}O_3N_2$	69.36	4.8	9.53	69.53	5.15	9.55
p-Nitro	100E + 70C	163–164[c]	159–160	138–160	$C_{17}H_{14}O_3N_2$	69.36	4.8	9.53	69.34	4.7	9.76
o-Amino	44E[d]	140–141		110–131	$C_{17}H_{16}ON_2$	77.23	6.1	10.61	77.25	6.2	10.49
m-Amino	33E[d]	114–115		[e]	$C_{17}H_{16}ON_2$	77.23	6.1	10.61	77.24	6.2	10.65
p-Amino	27E[d]	124–126		[e]	$C_{17}H_{16}ON_2$	77.23	6.1	10.61	77.17	6.0	11.26
-styryl)-quinoline											
2-(*o*-Nitro	100E		101–102[f]		$C_{17}H_{12}O_2N_2$	73.88	4.4	10.15	73.71	4.7	10.49
2-(*m*-Nitro	100E + 65C		157–158[g]		$C_{17}H_{12}O_2N_2$	73.88	4.4	10.15	73.94	4.5	10.40
2-(*p*-Nitro	100E + 92C		171–172[h]		$C_{17}H_{12}O_2N_2$	73.88	4.4	10.15	73.66	4.3	9.95

[a] By Dr. Carl Tiedcke, New York, N. Y. [b] Loew (*Ber.*, **36**, 1666 (1903)) gave m. p., 168°. [c] Bulach (*Ber.*, **20**, 2046 (1887)) gave m.p. 160°. [d] And washed with dry ether. [e] Would not solidify after melting. [f] Loew, Maurer and Starck (*Ber.*, **70**, 2054 (1937)) gave m. p., 103°; Noelting and Witte (*Ber.*, **39**, 2749 (1906)), m. p., 147°. [g] Wartanian gave m. p., 139°; Wallach and Wüsten (*Ber.*, **16**, 2007 (1883)), m. p., 154–155°; Taylor and Woodhouse, m. p., 156°; Noelting and Witte, m. p., 233°. [h] Bulach gave m. p., 164–165°.

The *m*- and *p*-**nitrophenylquinaldylcarbinols** were fairly soluble in cold chloroform, hot methanol, and hot ethanol; sparingly soluble in ether, cold methanol, cold ethanol, acetone, heptane or benzene. The *o*-**nitrophenylquinaldylcarbinol** was slightly more soluble in all the above solvents.

In an attempt to prepare *p*-nitrobenzylidene-diquinaldine, *p*-nitrobenzaldehyde was treated as above but with 2 proportions of quinaldine, giving an 82% yield (calculated on the aldehyde) of crude carbinol; m. p. 154–157° (softening at 144°). On recrystallization the colorless substance had m. p., 163–164° (fast), 159.5–160.5° (slow); its analysis showed it to be pure *p*-nitrophenylquinaldylcarbinol.

Anal. Calcd. for $C_{17}H_{14}N_2O_3$: C, 69.36; H, 4.8; N, 9.53. Found: C, 69.45; H, 5.0; N, 9.35.

Effect of Heat on the Nitrophenylquinaldylcarbinols.—Pure, recrystallized *p*-nitrophenylquinaldylcarbinol (3.5 g.) was heated under diminished pressure (34 mm.) in a bath until just molten; the temperature of the melt was then maintained at 155–157° during four and a half hours, after which the material was cooled and recrystallized; m. p., 168–170° (softening at 163°). It had therefore been mainly converted to the corresponding styryl derivative.

When the mother liquor from the preparation of the *p*-nitrophenylquinaldylcarbinol was evaporated to dryness, reheated as for the preparation of the carbinol, and the product isolated, the corresponding styryl compound was invariably obtained; m.p., 171–172°. If, however, the mother liquors from the preparation of the *o*- and *m*-nitrophenylquinaldylcarbinols, respectively, were treated in this manner, further crops of the pure carbinols were isolated.

Effect of Mineral Acid: (a) *p*-**Nitro Derivative.**—Commercial *p*-nitrobenzaldehyde (acid to congo red) was employed in an attempted preparation of the carbinol, as above. In less than one hour after heating had commenced, the mixture solidified and water was evolved. The solid was dissolved by shaking with chloroform plus water, the chloroform layer washed successively with sodium hydroxide solution and water, dried and evaporated to dryness. The yellow crystalline product was recrystallized and proved to be the corresponding styryl derivative; m. p., 171–172°.

(b) *m*-**Nitro Derivative.**—The preparation, as for the carbinol, was performed in the usual manner but using neutral *m*-nitrobenzaldehyde to which one drop of 0.1 *N* sulfuric acid was added before commencing the heating. The crude, yellow solid product had m. p. 137–150° (softening at 130°); on recrystallization from 10 volumes of ethanol plus 7.5 volumes of chloroform it gave yellow crystals; m. p. 145–150° (softening at 131°). It therefore consisted of a mixture of the styryl and carbinol derivatives. (A mixture of the pure carbinol with the pure styryl derivative had m. p., 134–141°.)

Acetylation of *m*-**Nitrophenylquinaldylcarbinol.**—To 3 g. of dry, recrystallized *m*-nitrophenylquinaldylcarbinol was added 25 cc. of dry pyridine, followed by 20 cc. of acetic anhydride, and the flask tightly stoppered. The solid dissolved slowly without any appreciable heat evolution and, after two and a half hours at room temperature, had formed a clear, very pale yellow solution which was kept overnight at room temperature and then poured slowly, with vigorous stirring, on to 500 cc. of chopped ice plus ice water. The colorless gum which first separated soon changed to perfectly colorless crystals. Sodium bicarbonate powder was now cautiously added, with stirring, until the aqueous solution was alkaline to red litmus, the suspension filtered, and the colorless crystals washed with water and dried; yield, quantitative. It was recrystallized from absolute ethanol (4 volumes) giving pale yellow crystals; m. p., 101–104°.

Anal. Calcd. for $C_{19}H_{16}N_2O_4$: C, 67.85; H, 4.8; N, 8.34. Found: C, 67.70; H, 5.0; N, 8.84.

On admixture of a sample with pure 2-(*m*-nitrostyryl)-quinoline, m. p., 143–148° (softening at 120°).

General Method for Preparation of the 2-(Mononitrostyryl)-quinolines.—The pure carbinol (5 g.) in 20 cc. of acetic anhydride[1] was gently boiled under reflux for two hours, the solution cooled and poured into one liter of ice plus water, with stirring. The product was filtered off, washed with water until the washings were neutral to litmus, and dried; yield, quantitative. The substance was then recrystallized (see Table I).

The *m*- **and** *p*-**nitrostyryl** derivatives were sparingly soluble in ether and heptane; the *o*-**nitrostyryl compound** was more soluble.

The *m*-**nitrostyryl** derivative was also prepared directly, by the method of Bulach[2]; a mixture of 21.1 g. of *m*-nitrobenzaldehyde, 20 g. of quinaldine, and 100 cc. of acetic anhydride was boiled under reflux for four hours, and the product isolated as above; yield, 89%.

Bromination of 2-(*m*-**Nitrostyryl)-quinoline.**—To a solution of 2-(*m*-nitrostyryl)-quinoline (5 g.) in 100 cc. of chloroform was added (dropwise, with swirling) a solution of 3.0 g. of bromine in 50 cc. of chloroform; a yellow precipitate formed after addition of about a third of the bromine solution. After addition of bromine had been completed, 150 cc. of water was added, followed by saturated sodium bicarbonate solution until alkaline; the solid then dissolved in the chloroform. The chloroform layer was

washed, dried, and evaporated to dryness, giving 7.3 g. of yellow crystals which were recrystallized from 10 volumes of ethanol plus 9.3 volumes of chloroform; m. p., 170–171°. Taylor and Woodhouse[2] give the same m. p.

Anal. Calcd. for $C_{17}H_{12}N_2O_3Br_2$: N, 6.43; Br, 36.67. Found: N, 6.61; Br, 36.85.

Bromination of *m*-Nitrophenylquinaldylcarbinol.—The carbinol (5 g.) in 325 cc. of chloroform was treated with bromine in chloroform as above, but no precipitate settled. After addition of the water and sodium bicarbonate solution, and drying with anhydrous sodium sulfate, an orange-colored precipitate formed on the sodium sulfate. The solid was filtered off, washed with water until free from sodium sulfate, and dried; wt., 0.8 g. It had an indefinite melting point, 137–185°, most of it melting at 153°.

Anal. Calcd. for $C_{17}H_{13}N_2O_2Br$: N, 7.84; Br, 22.37. Found: N, 8.29; Br, 16.00.

The dried chloroform solution was evaporated to dryness, giving a yellow-orange gum; wt., 5.2 g. This was treated with 15 cc. of chloroform, yielding 1 g. of white solid; m. p., above 200°.

Anal. Calcd. for $C_{17}H_{11}N_2O_2Br_3$: N, 5.44; Br, 46.55. Found: N, 6.24; Br, 45.46.

The mother liquor of this crop was evaporated to dryness and treated with ether and pentane, giving a further 0.6 g. of pale brown crystals; m. p., 110–120°. Its analysis indicated it to be slightly impure starting material.

Preparation of Monoaminophenylquinaldylcarbinols.—A mixture of the pure carbinol (5 g.) with 0.1 g. of Adams platinum catalyst was suspended in 100 cc. of methanol and shaken at room temperature with hydrogen in the Burgess–Parr apparatus. The initial pressure was approximately 39.5 lb. per sq. inch; as hydrogenation proceeded the sparingly soluble nitro derivative dissolved. After absorption of hydrogen was complete, or extremely slow, shaking was stopped, the catalyst filtered off and washed with methanol, and the filtrate plus washings evaporated to dryness. The product was recrystallized from boiling ethanol (see Table I), washed with dry ether and dried; yield, about 50%. All three amino derivatives were soluble in methanol, ethanol and chloroform; slightly soluble in ether or benzene; very sparingly soluble in carbon tetrachloride or heptane.

***p*-Aminophenylquinaldylcarbinol.**—The maximum yield was obtained when hydrogenation proceeded for three hours (but the pressure would continue to fall very slowly after the elapse of this period of time). The product was a sirup which was first obtained crystalline by adding a few cc. of dry ether. The pure substance was pale yellow-orange in color.

***o*-Aminophenylquinaldylcarbinol.**—Reduction was conducted for ninety minutes but there was no diminution in pressure during the last thirty minutes. The pure substance was colorless.

***m*-Aminophenylquinaldylcarbinol.**—Reduction was performed for three hours, the pressure remaining constant during the last thirty minutes. The pure substance was colorless.

Summary

1. The three mononitrophenylquinaldylcarbinols, and their corresponding styryl derivatives, have been prepared and some of their properties are described.

2. *m*-Nitrophenylquinaldylcarbinol has been successfully acetylated.

3. By catalytic hydrogenation of the nitro carbinols, the three monoaminophenylquinaldylcarbinols have been prepared.

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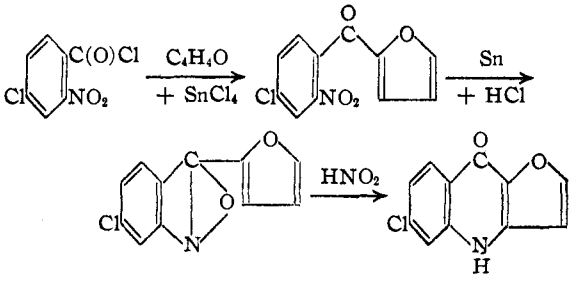
The Preparation of a Furo[3.2-b]quinolone

BY AVERY A. MORTON AND DOUGLAS BANNERMAN

Furo[3.2-b]quinolone is the furo analog of acridone. According to arguments presented in a previous paper[1] anisole and furan are comparable compounds and furan shows, to a greater degree than anisole, those reactions which are typical of aromatic compounds which contain methoxy groups. Hence furo[3.2-b]quinolone might also be regarded as the analog of 6-methoxyacridone.

Acridone and 6-methoxyacridone are important intermediates in the preparation of bacteriostatic and anti-malarial reagents. The object of this study is to prepare a compound which has the hitherto unknown furo[3.2-b]quinolone system for the ultimate purpose of comparing the physiological potency of derived compounds with those from the corresponding acridones and 6-methoxyacridones.

The compound selected for preparation was 6-chlorofuro[3.2-b]quinolone because it would be analogous to the intermediate now used in the preparation of atabrine. The steps employed utilize a furo nitrophenyl ketone and an anthranil as shown.



The anthranil was characterized by (a) a correct analysis, (b) its solubility in cold concentrated hydrochloric acid and precipitation on dilution, a behavior characteristic of all anthranils and (c) its conversion by means of a trace of nitrous acid to a higher melting isomer, the analog of acridone. The furoquinolone itself was characterized by its analysis, and by its possession of physical properties characteristic of acridones. The actual yield

(1) Morton and Patterson, THIS JOURNAL, **65**, 1346 (1943).