[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MARYLAND]

REACTIONS OF NAPHTHOQUINONES WITH MALONIC ESTER AND ITS ANALOGS. II. REACTIONS WITH ACETOACETIC ESTER AND PYRIDINE OR QUINOLINE[1, 2]

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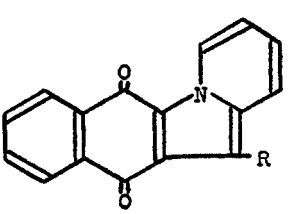
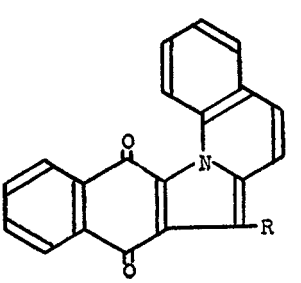
In the preceding paper of this series (1) it was found that 1,4-naphthoquinone and diethyl malonate in pyridine at room temperature underwent a Michael reaction in which both active hydrogens of the diethyl malonate were replaced by quinone groups. In the present study it was found that when ethyl acetoacetate together with a small amount of hydrochloric acid was used in place of the diethyl malonate orange needles were obtained in low yield. The same product was obtained in good yield by refluxing an alcoholic solution of 2,3-dichloro-1,4-naphthoquinone, ethyl acetoacetate, and pyridine. Since the product contained nitrogen in stable combination it is evident that the pyridine took part in the reaction to give a structure fundamentally different from that previously described.

The reactions of the nitrogen-containing compound and the numerous closely related compounds described below as well as the results of elementary analyses and alkoxyl determinations are consistent with the proposal that it is 1-carbethoxy-2,3-phthaloylpyrrocoline (I). Determination of the molecular weight of I by the Beckmann method and of both I and V by the Rast method gave values within 5% of those calculated.



I R = $COOC_2H_5$
II R = $COOCH_3$
III R = COOH
IV R = $CONH_2$



V R = $COOC_2H_5$
VI R = $COOCH_3$

Proof that the ethyl acetoacetate underwent cleavage was obtained when it was found that ethyl benzoylacetate gave the same product, (I). Methyl acetoacetate was found to give the analogous carbomethoxyl compound (II) and quinoline with ethyl acetoacetate produced 1-carbethoxy-2,3-phthaloyl-5,6-

[1] Presented at the W. E. Bachmann Memorial Session, Organic Chemistry Division, American Chemical Society, Chicago Meeting, September 8, 1953.

[2] From the Ph.D. thesis of Raymond W. Luckenbaugh, May, 1952, and the M.S. Thesis of Raymond L. Erickson, Jan., 1950.

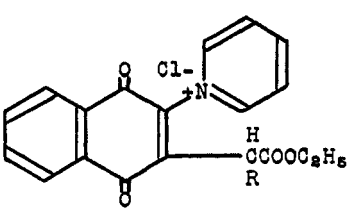
TABLE I

PYRROCOLINES AND BENZOPYRROCOLINES FROM 2,3-DICHLORO-1,4-NAPHTHOQUINONE

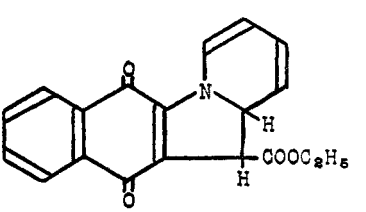
ACTIVE METHYLENE COMPOUND	PRODUCT	RECRYST. SOLVENT	M.P., °C.	YIELD, %	COLOR AND FORM	ANALYSES							
						Calculated				Found[a]			
						C	H	N	RO—	C	H	N	RO—
$CH_3COCH_2COOC_2H_5$	I	Ethanol	157–158	49	Orange needles	71.47	4.10	4.39	14.11	71.45	4.27	4.58	14.11
$C_6H_5COCH_2COOC_2H_5$	I	Ethanol	157–158	16	Orange needles								
$CH_3COCH_2COOCH_3$	II	Acetic acid	190–191[b]	51	Yellow needles	70.82	3.63	4.59	10.17	71.11	3.67	4.65	10.32
$CH_3COCH_2COOC_2H_5$	V	Chloro-benzene	238–239	45	Orange plates	74.79	4.09	3.79	12.20	74.41	4.34	3.89	12.15
$CH_2(COOC_2H_5)_2$	V	Dioxane	238–239	11	Yellow needles	74.79	4.09	3.79	12.20	74.47	4.40	4.00	12.13
$CH_3COCH_2COOCH_3$	VI	*o*-Xylene	244–245	39	Orange plates	74.36	3.69	3.94	8.73	74.42	3.73	4.02	8.81
$CH_2(COOCH_3)_2$	VI	*o*-Xylene	244–245	20	Orange plates								

[a] Averages of duplicates. [b] With decomposition.

benzopyrrocoline (V). Cleavage of the active methylene compounds was confirmed by the finding that V was also obtained when diethyl malonate replaced the ethyl acetoacetate while the carbomethoxyl analog (VI) was produced from either dimethyl malonate or methyl acetoacetate. In all these cases 2,3-dichloro-1,4-naphthoquinone was used in preference to the unsubstituted quinone. Yields and other pertinent data for these primary reaction products are listed n Tab le I.



VII R = $COCH_3$
VIII R = H

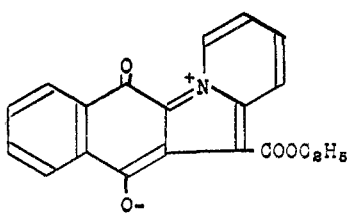


IX

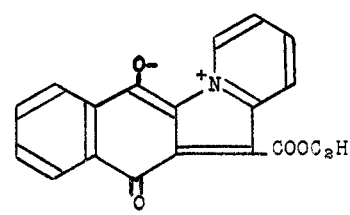
The presence of the quinone nucleus in V was demonstrated by reductive acetylation to the diacetate of the corresponding hydroquinone. Upon heating I or V with concentrated nitric acid on a hot plate until dry a sublimate of phthalic anhydride was obtained. A mono-oxime and a mono-2,4-dinitrophenylhydrazone of I were prepared. It is suggested that the carbonyl group farthest from the nitrogen reacts preferentially since it is less hindered sterically.

Hydrolysis of the ethyl ester (I) with alcoholic sodium ethoxide gave the acid (III) which was converted to the acid chloride and the amide (IV) in standard fashion.

It is proposed that the formation of I proceeds *via* displacement of one of the chlorine atoms of the dichloroquinone by ethyl acetoacetate and displacement of the other by pyridine to give the key intermediate (VII). Michel (2) has reported the occurrence of the first type of displacement and a reaction essentially identical with the second has been described by Ullmann and Ettisch (3). Cleavage of the acetyl group of VII to form VIII would be expected to occur readily since the carbon to which this group is attached holds two additional groups which attract electrons strongly. A negative group attack at the activated position of the pyridine ring by the carbanion formed by loss of a hydrogen from the highly activated methylene group of VIII would give IX. Alternatively IX might be formed by loss of a molecule of water from the pseudo base derived from VIII. Successive α,γ shifts of the two hydrogen atoms on the five-membered ring of IX would produce the hydroquinone corresponding to I. A third possibility is that the pseudo base derived from VIII is oxidized to the pyridone which undergoes an intramolecular Knoevenagel condensation to give I. The formation of I, by whatever route, is doubtlessly facilitated by the resonance stabilization arising from contribution of structures X and XI.

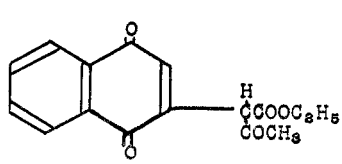


X

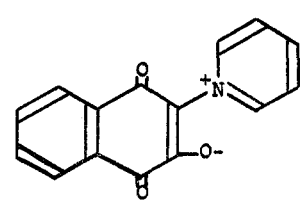


XI

A closely related series of reactions may be proposed for the formation of I from the unsubstituted 1,4-naphthoquinone. A Michael reaction followed by oxidation of the resultant hydroquinone would produce XII which in the presence of pyridine and hydrochloric acid might well give the hydroquinone from which VII would be obtained by oxidation. The conversion of quinones to pyridinium salts under closely similar conditions has been reported (4, 5). The correlation of the low (14%) yield of I obtained from the free quinone for which three oxidations by excess quinone may be required with the much higher (49%) yield from the dichloroquinone for which only one such oxidation is proposed may be significant.



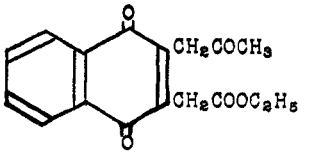
XII



XIII

An attempted reaction of diethyl malonate, pyridine, and the dichloroquinone produced the hydrate of compound XIII, which has been previously synthesized

(3, 6). The experiment under the same conditions except using ethyl acetoacetate gave I as described above. These results are consistent with the fact that diethyl malonate is less reactive than ethyl acetoacetate. As previously pointed out, however, V was obtained from the reaction using diethyl malonate and quinoline. This may be correlated with the fact that quinoline does not form the analog of XIII with 2,3-dichloro-1,4-naphthoquinone (3).



XIV

The reaction of potassium 1,4-naphthoquinone-2-sulfonate and ethyl acetoacetate in aqueous alcoholic alkali was tried in an attempt to extend the reaction previously reported (1) for diethyl malonate. Maroon needles were obtained which contrary to expectations proved to be compound XIV which has been previously prepared from 2,3-dichloro-1,4-naphthoquinone (2). It is interesting that in the formation of this compound one of the added ethyl acetoacetate moieties loses the acetyl group on cleavage while the other loses the carbethoxyl group. It was found that 2-bromo-1,4-naphthoquinone and also 1,4-naphthoquinone itself reacted to give XIV under similar conditions. The yields obtained from the three different quinones were 40, 32, and 25% respectively.

EXPERIMENTAL[3, 4]

Syntheses of compounds I, II, V, and VI. The following procedure was used for all the experiments of Table I. To a mixture of 0.50 g. of 2,3-dichloro-1,4-naphthoquinone and 5 ml. of the designated active methylene compound dissolved in 25 ml. of absolute alcohol was added 7 ml. of pyridine (for compounds I and II) or quinoline (for compounds V and VI). The resultant solution was refluxed for 4 hrs. After cooling the reaction mixture in an ice-bath the precipitate was filtered off. One recrystallization from the indicated solvent gave the designated yields of products.

Compound I was also prepared from the unsubstituted quinone as follows. 1,4-Naphthoquinone (3 g.) was dissolved at 40° in a solution of 15 ml. of pyridine and 0.5 ml. of 6 *N* hydrochloric acid. Upon the addition of 5 ml. of ethyl acetoacetate, with swirling, heat was evolved and the mixture turned dark. After standing overnight at room temperature the mixture was placed in the refrigerator for 5 days. The orange-brown solid (1.0 g.) was filtered off and recrystallized twice from ethanol using charcoal for decolorization. The resultant orange needles weighed 0.84 g. (14%) and melted at 156–157°. Two more recrystallizations raised the melting point to 157–158°.

No depression in melting point was observed when mixtures of this product and the products from each of the first two experiments of Table I were melted. Similarly mixtures of products from the fourth and fifth experiments and from the sixth and seventh experiments of Table I melted at the same temperatures as those tabulated for the unmixed materials.

The molecular weights of compounds I and V were determined by the Rast method using camphor as the solvent. Several determinations in each case gave average values of 330

[3] All melting points are corrected.

[4] We wish to thank Prof. Mary Aldridge for all analyses reported herein.

and 376; the calculated values are 319 and 369, respectively. An average value of 322 was obtained for compound I by the Beckman method using benzene as the solvent.

Oxidations. A solution of 0.10 g. of compounds I or V and 1.0 ml. of concentrated nitric acid contained in a 5-ml. beaker covered with a watch glass was evaporated to dryness on a hot plate.[5] The white, crystalline sublimate which collected on the cover was found to melt at 129–130° both alone and when mixed with authentic phthalic anhydride.

Carbonyl derivatives of I. A mixture of 0.20 g. of compound I, 0.15 g. of hydroxylamine hydrochloride, and 30 ml. of 95% ethanol was heated under reflux for 1.5 hrs. and allowed to stand overnight at room temperature. Upon filtration and washing of the precipitate with 95% ethanol 0.13 g. (62%) of orange needles which melted at 205–207° (dec.) was obtained. Treatment with carbon and recrystallization from glacial acetic acid gave 0.07 g. of yellow needles which melted at 215–217° (dec.)

Anal. Calc'd for $C_{19}H_{14}N_2O_4$: C, 68.26; H, 4.22; N, 8.38; C_2H_5O, 13.49.
Found: C, 68.50, 68.24; H, 4.24, 4.08; N, 8.14, 8.12; C_2H_5O, 13.61.

A mixture of 50 ml. of 95% ethanol, 0.20 g. of I, and 0.30 g. of 2,4-dinitrophenylhydrazine was heated to boiling. After solution was effected 5 drops of concentrated hydrochloric acid were added and heating was continued until a yellow solid separated. The crude product (0.45 g.) was recrystallized from 12 ml. of nitrobenzene and was washed with 95% ethanol and ether. Yellow needles which melted at 261° (dec.) were obtained in quantitative yield (0.31 g.).

Anal. Calc'd for $C_{25}H_{17}N_5O_7$: C, 60.12; H, 3.43; N, 14.01; C_2H_5O, 9.02.
Found: C, 60.24, 60.06; H, 3.52, 3.64; N, 13.70, 13.50; C_2H_5O, 9.09, 9.20.

Reductive acetylation of compound V. One gram of zinc dust was added gradually over one-half hour to a refluxing solution of 0.3 g. of V and 20 ml. of a 1:1 solution of pyridine and acetic anhydride. After an additional one-half hour of refluxing the solution was poured into 200 ml. of cold water. The yellow solid was filtered off, washed with water, and dried. The crude product (0.46 g.) was extracted with 95% ethanol in a Soxhlet apparatus for 6 hrs. and the 0.21 g. of undissolved yellow powder was recrystallized from a large volume of benzene. A 38% yield (0.14 g.) of bright yellow prisms which melted at 239.5–240.5° was obtained. A solution of this product in benzene or ethanol shows a green fluorescence.

Anal. Calc'd for $C_{27}H_{21}NO_6$: C, 71.20; H, 4.65; N, 3.08; C_2H_5O, 9.89.
Found: C, 71.21, 71.21; H, 4.78, 4.72; N, 3.19, 3.37; C_2H_5O, 9.53, 9.78.

Preparation of the acid III *and the amide* IV. A solution of 1.0 g. of I in 200 ml. of hot absolute alcohol was poured into a cold solution prepared from 0.80 g. of clean sodium and 40 ml. of absolute alcohol. Upon refluxing the reaction mixture for 10 min. a red, gelatinous mass precipitated. This was filtered off and washed with the minimum amount of cold absolute alcohol. The resultant 1.05 g. of red powder was extracted with glacial acetic acid in a Soxhlet apparatus for 14 hrs. The red solution was allowed to stand several days whereupon 0.70 g. (77%) of maroon needles which melted at 314.5° (dec.) and which were only very slightly soluble in the common organic solvents were obtained.

Anal. Calc'd for $C_{17}H_9NO_4$: C, 70.10; H, 3.12; N, 4.81.
Found: C, 70.01; H, 3.39; N, 4.86.

A mixture of 0.30 g. of the pure acid (III) and freshly distilled thionyl chloride was heated under reflux for 4 hrs. After the excess thionyl chloride was carefully boiled off the solid residue was cooled in an ice-bath while 10 ml. of concentrated ammonium hydroxide was added dropwise. After the mixture was allowed to stand for two days the solid was filtered off and washed by trituration with water. The dried powder was recrystallized from nitrobenzene to give 0.02 g. (7%) of maroon needles which melted at 302° (dec.).

Anal. Calc'd for $C_{17}H_{10}N_2O_3$: C, 70.34; H, 3.47; N, 9.65.
Found: C, 69.86; H, 3.56; N, 9.12.

Synthesis of compound XIII. When diethyl malonate was used with pyridine and 2,3-dichloro-1,4-naphthoquinone, under the conditions given above for the experiments of

[5] This facile procedure was first developed for a related compound by Mr. R. W. Storherr in these laboratories.

Table I, 0.20 g. of light yellow needles which melted at 288–289° were obtained. The results of elementary analysis of this product agreed with the values calculated for the monohydrate of compound XIII.

Anal. Calc'd for $C_{15}H_9NO_3 \cdot H_2O$: C, 66.91; H, 4.12; N, 5.20.
Found: C, 67.41; 67.37; H, 4.03, 4.05; N, 5.27, 5.23.

A mixture of this monohydrate and a sample of the anhydrous compound (XIII), m.p. 292°, prepared by the method Ullmann and Ettisch (3, 6) melted at 288–290°. The monophenylhydrazone prepared in quantitative yield from the monohydrate melted at 252–253° [lit. value, 253° (3)] and the quinoxaline derivative prepared in 60% yield from the monohydrate melted at 304–305° [lit. value, 305° (3)].

Syntheses of the ethyl ester of (2-acetonyl-1,4-naphthoquinone-3)-acetic acid (XIV). A solution of 0.5 g. of potassium 1,4-naphthoquinone-2-sulfonate monohydrate in 30 ml. of distilled water warmed to 55° was added with swirling to a solution of 4 ml. of ethyl acetoacetate, 4 ml. of 10% aqueous tetramethylammonium hydroxide, and 6 ml. of 95% alcohol. A dark blue color appeared which changed rapidly to a dark red. After standing overnight in the refrigerator the reaction mixture was acidified with hydrochloric acid, to produce XIV from what appears to be a salt of the enol form, and the crystalline precipitate was filtered off and washed with aqueous alcohol. When the 0.30 g. of crude material was recrystallized from 95% alcohol 0.20 g. (40%) of dark red needles with a green surface luster were obtained, m.p. 155–157°. A sample recrystallized five times more melted at 157–158° and analyzed as follows:

Anal. Calc'd for $C_{17}H_{16}O_5$: C, 68.00; H, 5.33.
Found: C, 68.08, 68.18; H, 5.43, 5.30.

Since the 2-bromo-1,4-naphthoquinone prepared by the general method of Chang (8) melted nearly 10° higher than he reported, the details of the procedure used are given. A solution of 3.0 g. of 1,4-naphthoquinone in 35 ml. of glacial acetic acid was treated with bromine while cooling under a water tap until no more bromine appeared to be absorbed. After the reaction mixture stood for 2 hrs. it was heated to about 60° on a steam-bath while excess bromine was removed with the aid of a current of air. Then 3 g. of anhydrous sodium acetate was added and the mixture was heated for 1 hr. on the steam-bath. The mixture containing precipitated sodium bromide was poured into about ten volumes of water and the yellow precipitate was filtered off. Recrystallization of the 4.1 g. of crude product from alcohol gave 2.75 g. (61%) of yellow needles which melted at 136–139° [lit. values, 128–129° (8), and 129–130° (9)].

Anal. Calc'd for $C_{10}H_5BrO_2$: C, 50.63; H, 2.11; Br, 33.76.
Found: C, 50.96, 50.89; H, 2.34, 2.41; Br, 33.62, 33.97.

One gram of this 2-bromo-1,4-naphthoquinone dissolved in 50 ml. of 95% ethanol at 50° was treated with a solution of 4 ml. of ethyl acetoacetate, 5 ml. of 10% aqueous potassium hydroxide, and 4 ml. of 95% alcohol. After the reaction mixture stood at room temperature for 16 hrs. the precipitate was filtered off. It was heated with about 500 ml. of water, traces of solid were filtered off, and the filtrate was acidified with hydrochloric acid. The flocculent precipitate was recrystallized from 95% alcohol; 0.40 g. (32%) of red needles which melted at 156–158° were obtained.

A solution of 4 ml. of ethyl acetoacetate, 0.07 g. of sodium hydroxide, and 6 ml. of absolute alcohol was added with swirling to 0.40 g. of 1,4-naphthoquinone dissolved in 20 ml. of absolute alcohol at 40°. After the mixture was allowed to stand for 48 hrs. at room temperature the precipitate was filtered off. The 0.29 g. of crude product was purified by solution in hot water, followed by acidification and recrystallization as before. A 25% yield (0.19 g.) of dark red needles which melted at 156–158° was obtained.

Compound XIV was also synthesized from 2,3-dichloro-1,4-naphthoquinone in 50% yield by the method of Michel (2). The product melted at 156–158° both alone and when mixed with each of the products obtained by the foregoing three methods of synthesis.

An attempt was made to compare the reactivities of the above four quinones. Because of differing solubilities it was impractical to use identical conditions but a rough test with excess ethyl acetoacetate in aqueous ethanol at 40° made alkaline with sodium hydroxide

indicated that the order of decreasing reactivity was: potassium 1,4-naphthoquinone-2-sulfonate monohydrate, 2-bromo-1,4-naphthoquinone, 2,3-dichloro-1,4-naphthoquinone, and 1,4-naphthoquinone. The time required for completion of the reaction under these conditions varied from about 2 to about 48 hrs.; the yields were 29, 32, 35, and 10%, respectively.

Acknowledgments. We wish to thank the Research Corporation and the National Institutes of Health for generous financial support which greatly aided the progress of this work.

SUMMARY

Upon refluxing a mixture of ethyl acetoacetate, pyridine, and 2,3-dichloro-1,4-naphthoquinone an orange solid for which structure I is proposed is obtained in 49% yield. Quinoline reacts satisfactorily in place of pyridine to give V. Active methylene compounds which may be used in place of ethyl acetoacetate to form the same or analogous products are ethyl benzoylacetate, methyl acetoacetate, diethyl malonate, and dimethyl malonate. A number of derivatives of I and its analogs have been prepared. The results of elementary analyses and molecular weight and alkoxyl determinations are consistent with those calculated for the proposed structures. A reaction sequence for the formation of I is proposed.

It was found that the interesting dark red compound (XIV) first obtained by Liebermann (7) from ethyl sodioacetoacetate and 2,3-dichloro-1,4-naphthoquinone is also produced when potassium 1,4-naphthoquinone-2-sulfonate or 2-bromo-1,4-naphthoquinone or 1,4-naphthoquinone itself is used in place of the dichloroquinone.

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