

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

Reactions of Naphthoquinones with Malonic Ester and its Analogs. IV. A Synthesis of 2,3-Disubstituted-4,5-phthaloylfurans

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A 78% yield of 2-phenyl-3-cyano-4,5-phthaloylfuran (X) is obtained readily upon warming benzoylacetonitrile and 2,3-dichloro-1,4-naphthoquinone (I) with pyridine in ethanol. With tributylamine in place of the pyridine analogous phthaloylfurans (XI and XII) are obtained from acetyl- or benzoylacetone and the dichloroquinone in about 15% yield. The same three (X, XI and XII) and two additional furans (XIII and XIV) are obtained, in 35% average yield, by cyclization of 3-(α -cyano- α -benzoylmethyl)-2-chloro-1,4-naphthoquinone and its analogs (V to IX) with tributylamine. Proof of structure was accomplished by alkaline hydrolysis of the furan ring of 2-methyl-3-acetyl-4,5-phthaloylfuran (XI) with spontaneous loss of an acetyl group to give the known 2-hydroxy-3-acetyl-1,4-naphthoquinone (III) in 79% yield. The ultraviolet absorption spectra of the products were also consistent with the phthaloylfuran structures.

It has been found that 2-phenyl-3-cyano-4,5-phthaloylfuran (X) is obtained in 78% yield upon heating under reflux a mixture of benzoylacetonitrile, 2,3-dichloro-1,4-naphthoquinone (I) and pyridine in ethanol. When a number of other active methylene compounds were employed in place of the benzoylacetonitrile the pyridine took part in the reaction and phthaloylpyrrocolines were formed as described in the previous paper of this series.² The cause of this exceptional behavior of benzoylacetonitrile is not readily apparent; in fact when benzoylacetonitrile was employed with isoquinoline in place of pyridine a 68% yield of the expected phthaloylbenzopyrrocoline was obtained.² If pyrrocoline formation is prevented by using tributylamine in place of pyridine, phthaloylfurans XI and XII are obtained in about 15% yield from acetylacetone or benzoylacetone and the dichloroquinone. Two of the phthaloylfurans X and XI were smoothly reductively acetylated to the corresponding hydroquinone diacetates.

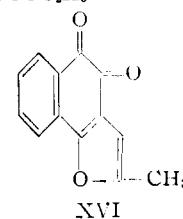
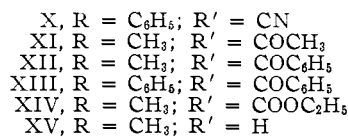
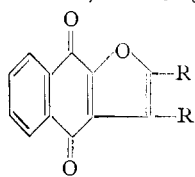
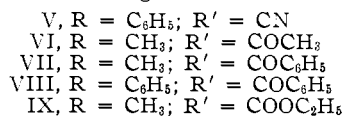
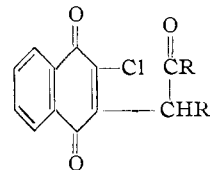
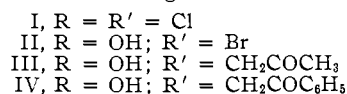
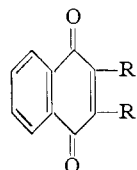
When benzoylacetonitrile was used with 2-hydroxy-3-bromo-1,4-naphthoquinone (II) in place of the dichloroquinone the same furan (X) was obtained in 34% yield.

The foregoing three (X, XI and XII) and two additional furans (XIII and XIV) have been readily obtained by treatment of 3-(α -benzoyl- α -cyanomethyl)-2-chloro-1,4-naphthoquinone and its analogs (V to IX) with a tertiary amine. Two of these intermediates (V and VIII) are new; they were prepared by extension to benzoylacetonitrile and dibenzoylmethane of the published procedures for condensing other active methylene compounds with 2,3-dichloro-1,4-naphthoquinone by treatment with sodium ethoxide.^{3,4} The intermediates employed, the furans obtained from them and the yields of pure, recrystallized product were as follows: V \rightarrow X, 67%; VI \rightarrow XI, 43%; VII \rightarrow XII, 30%; VIII \rightarrow XIII, 26%; and IX \rightarrow XIV, 13%. This two-step synthesis of phthaloylfurans appears to be the more general since attempts to prepare the two additional products (XIII and XIV) by the one-step process first described were unsuccessful. The two processes very probably proceed *via* the same intermediates.

(1) From the Ph.D. thesis of Rip G. Rice, April, 1957.

(2) E. F. Pratt, R. G. Rice and R. W. Luckenbaugh, *THIS JOURNAL*, **79**, 1212 (1957).(3) F. Michel, *Ber.*, **33**, 2402 (1900).(4) B. Suryanarayana and B. D. Tilak, *Proc. Indian Acad. Sci.*, **38A**, 534 (1953).

It is of interest that the intermediate 3-(α -benzoyl- α -cyanomethyl)-2-chloro-1,4-naphthoquinone and its analogs (V to IX) are stable to the strongly basic sodium ethoxide used in their formation although they are converted to the phthaloylfurans X to XIV by the relatively weakly basic tertiary



amines. If these intermediates are considered to be acid chlorides, to which they stand in vinylogous relationship, their cyclization to the furans by the amines involves O-acylation while their formation from the dichloroquinone by the alkoxide involves C-acylation; the selective O-acylation and C-acylation of ethyl acetoacetate under corresponding conditions is well known.^{5,6}

(5) W. J. Hickinbottom, "Reactions of Organic Compounds," Longmans, Green and Co., London, 1936, pp. 104, 105.

(6) R. C. Fuson, "Advanced Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1950, p. 426.

Another relationship between O-acylation and the cyclization to furans is noteworthy. When in three parallel experiments the reaction of the dichloroquinone and benzoylacetonitrile was attempted in the presence of pyridine, tributylamine and dimethylaniline the yields of furan X were 78, 57 and 0%; when the reaction of benzoyl chloride and ethyl benzoylacetate was attempted by Wright and McEwen⁷ in the presence of pyridine, triethylamine and dimethylaniline the yields of O-acylated product were 76, 49 and 0%.

Upon alkaline hydrolysis of 2-methyl-3-acetyl-4,5-phthaloylfuran (XI) cleavage of the furan ring occurred accompanied by spontaneous loss of an acetyl group to give the known 2-hydroxy-3-acetyl-1,4-naphthoquinone (III) in 79% yield. The procedure was based on that of Hooker and Steyermark⁸ for hydrolysis, without cleavage, of 2-methyl-4,5-phthaloylfuran to the same product. Following their procedures the hydroxyacetylquinone III was characterized by cyclization to the *o*-quinonylfuran XVI which in turn was isomerized to 2-methyl-4,5-phthaloylfuran (XV).⁸ Alkaline hydrolysis and cleavage of the methylcarbomethoxyfuran (XIV) also gave the hydroxyacetylquinone (III) and in analogous fashion the phenylbenzoylfuran (XIII) was converted to the known 2-hydroxy-3-phenacyl-1,4-naphthoquinone (IV). It is felt that the phthaloylfuran ring system is adequately established by these conversions.

Except for the 3-(α -acetyl- α -benzoylmethyl)-2-chloro-1,4-naphthoquinone (VII) there is no serious question concerning the direction of enolization of these intermediates (V to IX) so that the identity of the R and R' groups in the furans resulting from their cyclization is established. Since in benzoylacetone enolization of the carbonyl of the acetyl group predominates over that of the benzoyl group⁹ it is probable that the intermediate derived from it (VII) would enolize in analogous fashion to form the 2-methyl-3-benzoylfuran (XII) upon cyclization. This structure XII rather than the alternative 2-phenyl-3-acetyl-4,5-phthaloylfuran is more conclusively established, however, by the fact that the ultraviolet absorption spectrum is very similar to those of the three other furans with methyl groups at the 2-position (XI, XIV and XV) and very different from those of the two furans (X and XIII) with phenyl groups at the 2-position (*cf.* Table I of the Experimental section).

The fact that the peaks at the three lower wave lengths, *i.e.*, 250, 291 and 335 $m\mu$, for 2-methyl-4,5-phthaloylfuran (Table I) are affected very little by introduction of benzoyl, acetyl or carbomethoxyl groups at the 3-position is consistent with the identification of the high intensity 250 $m\mu$ and the low intensity 335 $m\mu$ peaks with the 1,4-naphthoquinone chromophore¹⁰ and with the proposal that the 291 $m\mu$ peak may be the result of bathochromic shifts of the peaks at about 280 $m\mu$ reported for 2-hydroxy-¹¹ and 2-methoxy-1,4-naphthoquinone.¹²

The highest wave length (382 $m\mu$) peak for 2-methyl-4,5-phthaloylfuran, on the other hand, undergoes distinct hypsochromic shifts when the substituents are introduced at the 3-position; analogous shifts of high wave length peaks which were found to be dependent on the structure of the entire molecule of related 1,4-naphthoquinones have been reported.¹⁰

Examination of scale models suggests that steric interference between the phenyl and benzoyl groups of 2-phenyl-3-benzoyl-4,5-phthaloylfuran (XIII) is at least partially responsible for the great difference between its spectrum and that of the 3-cyano analog X; similar effects of steric hindrance in 3-benzoyl-2,5-diphenylfuran have been reported.^{13,14}

The most closely related synthesis of which we are aware is the preparation, in unspecified yield, of two tetracyclic furans from 2,3-dichloro-1,4-naphthoquinone and a pyrazolone or a pyridone.¹⁵ Although the possibility of employing the common acyclic active methylene compounds has been previously considered^{15,16} they appear not to have been used successfully heretofore.

Experimental¹⁷

One-step Routes to 4,5-Phthaloylfurans.—To a mixture of 0.5 g. of 2,3-dichloro-1,4-naphthoquinone (I), 25 ml. of absolute ethanol and 0.5 g. of benzoylacetonitrile was added with stirring 5 ml. of tributylamine and the resultant mixture was heated under reflux 4 hr. with continued stirring. The mixture was cooled overnight in the refrigerator and the solid was filtered off, washed once with a little absolute ethanol and several times with ether, dried and recrystallized from 1-nitropropane. Yellow needles of 2-phenyl-3-cyano-4,5-phthaloylfuran (X) which melted at 252.0–253.0° and which weighed 0.39 g. were obtained. *Anal.* Calcd. for C₁₅H₉NO₃: C, 76.25; H, 3.03. Found: C, 76.25; H, 3.01. When 5 ml. of pyridine was substituted for the tributylamine the yield rose to 0.51 g.; with dimethylaniline under the same conditions no crystalline product was obtained.

The use of 0.5 g. of benzoylacetone in place of the benzoylacetonitrile in the procedure of the preceding paragraph, with tributylamine as the base, gave upon recrystallization from ethyl acetate 0.090 g. of 2-methyl-3-benzoyl-4,5-phthaloylfuran (XII) as tiny yellow plates which melted at 252.5–253.5°. *Anal.* Calcd. for C₂₀H₁₂O₄: C, 75.94; H, 3.83. Found: C, 75.74; H, 3.59.

When 4 ml. of acetylacetone was substituted for the 0.5 g. of benzoylacetonitrile in the procedure of the first paragraph, using tributylamine as the base, there was obtained upon recrystallization from ethyl acetate 0.083 g. of pale yellow needles of 2-methyl-3-acetyl-4,5-phthaloylfuran (XI) which melted at 202–203°. *Anal.* Calcd. for C₁₅H₁₀O₄: C, 70.86; H, 3.96. Found: C, 70.86; H, 3.86.

Replacement of the dichloroquinone in the procedure of the first paragraph by 0.5 g. of 2-hydroxy-3-bromo-1,4-naphthoquinone (II),¹⁸ using pyridine as the base and refluxing 16 hr., gave upon recrystallization from 1-nitropropane 0.20 g. of XI which melted at 252.0–253.0° both alone

(11) C. Dalglish, *THIS JOURNAL*, **72**, 4863 (1950).

(12) J. E. Little, T. J. Sproston and M. W. Foote, Jr., *J. Biol. Chem.*, **174**, 338 (1948).

(13) C. Dien and R. E. Lutz, *J. Org. Chem.*, **21**, 1501 (1956).

(14) We wish to thank Dr. Darrell V. Sickman of the U. S. Naval Ordnance Laboratory for the use of the Cary recording spectrophotometer, and Dr. Mortimer J. Kamlet of the same laboratory for aid in interpreting the spectra.

(15) B. Eistert, *Chem. Ber.*, **80**, 47 (1947).

(16) B. Suryanarayana and B. D. Tilak, *Proc. Indian Acad. Sci.*, **39A**, 185 (1954).

(17) All melting points are corrected. We are indebted to Professor Kathryn Gerdeman for the analyses. Most of the analytical data are averages of duplicates.

(18) Prepared as by G. Heller, H. Arnold and J. Schmidt, *Z. angew. Chem.*, **43**, 1132 (1930).

(7) P. E. Wright and W. E. McEwen, *THIS JOURNAL*, **76**, 4540 (1954).

(8) S. C. Hooker and A. Steyermark, *ibid.*, **58**, 1202 (1936).

(9) R. A. Morton, A. Hassan and T. C. Calloway, *J. Chem. Soc.*, 853 (1939).

(10) C. J. Spruit, *Rec. trav. chim.*, **68**, 311 (1949).

and when mixed with the material obtained as described above.

Two-step Route to 4,5-Phthaloylfurans.—The 3-(α,α -diacetylmethyl)- and the 3-(α -acetyl- α -benzoylmethyl)-2-chloro-1,4-naphthoquinone (VI and VII) were prepared from 2,3-dichloro-1,4-naphthoquinone and acetyl- or benzoylacetone by the procedure of Michel.³ Michel reports that when VII was first isolated it melted at 82° but upon recrystallization from methanol the melting point rose to 109°. Attempts to raise the melting point of our product above 81.5–82.5° were unsuccessful, but it underwent conversion to the furan XII satisfactorily and it had the desired carbon, hydrogen and chlorine content. *Anal.* Calcd. for C₂₀H₁₃ClO₄: C, 68.09; H, 3.71; Cl, 10.05. Found: C, 68.14; H, 4.03; Cl, 9.80.

Extension of the Michel procedure to benzoylacetonitrile gave, upon recrystallization from ethyl acetate, a 49% yield of 3-(α -benzoyl- α -cyanomethyl)-2-chloro-1,4-naphthoquinone (V) as minute yellow needles which melted at 182.5–183.5°. *Anal.* Calcd. for C₁₉H₁₀ClNO₃: C, 67.97; H, 3.00. Found: C, 67.98; H, 2.81. Similar extension of the procedure to dibenzoylmethane gave, after recrystallization from 95% ethanol, pale yellow needles of 3-(α,α -dibenzoylmethyl)-2-chloro-1,4-naphthoquinone (VIII) in 26% yield, m.p. 182.5–183.5°. *Anal.* Calcd. for C₂₈H₁₈ClO₄: C, 72.38; H, 3.64. Found: C, 72.46; H, 3.63.

In our hands the procedure of Suryanarayana and Tilak⁴ for the preparation of 3-(α -acetyl- α -carbethoxymethyl)-2-chloro-1,4-naphthoquinone (IX) proved to be superior to that of Michel.³

The phthaloylfuran X was prepared using 0.5 g. of the intermediate V in place of both the quinone and the active methylene compound of the procedure of the first paragraph employing pyridine as the base; the other four intermediates VI through IX were similarly converted to the phthaloylfurans XI through XIV employing tributylamine as the base. For the first three products (X, XI and XII) the method of recrystallization was identical with that already described for the one-step route and in each case the product from the two routes melted at the same temperature both alone and in admixture. The 2-methyl-3-carbethoxy-4,5-phthaloylfuran (XIV) upon recrystallization from ethyl acetate-petroleum ether gave pale yellow needles (0.059 g.) which melted at 163.0–163.5°. *Anal.* Calcd. for C₁₆H₁₂O₅: C, 67.60; H, 4.26; C₂H₅O, 15.85. Found: C, 67.85; H, 4.79; C₂H₅O, 15.66. Recrystallization of 2-phenyl-3-benzoyl-4,5-phthaloylfuran (XIII) from the same solvent mixture gave 0.12 g. of minute yellow needles which melted at 231.0–231.5°. *Anal.* Calcd. for C₂₅H₁₄O₄: C, 79.36; H, 3.73. Found: C, 79.25; H, 3.53.

Reductive Acetylation.—One gram of zinc dust was added gradually over 15 min. to a refluxing solution of 0.30 g. of X in 20 ml. of 1:1 pyridine:acetic anhydride. After refluxing was continued for 1 hr. the solution was decanted from the remaining zinc into about 250 ml. of water. The mixture was allowed to stand overnight then filtered and the solid recrystallized from ethyl acetate. A 59% yield (0.23 g.) of 2-phenyl-3-cyano-4,9-diacetoxynaphtho[2,3-b]furan was obtained as light yellow needles which melted at 272.5–273.5°. *Anal.* Calcd. for C₂₂H₁₃NO₅: C, 71.68; H, 3.92; N, 3.64. Found: C, 71.73; H, 4.02; N, 4.01.

Reductive acetylation of XI by the same procedure gave an 85% yield of 2-methyl-3-acetyl-4,9-diacetoxynaphtho[2,3-b]furan as pale yellow needles which were recrystallized from 95% ethanol. Apparently allotropic modifications of this compound were obtained, for crystals melting in the neighborhood of 179–182° were repeatedly obtained which in all cases upon being allowed to resolidify remelted at 187–188°. *Anal.* Calcd. for C₁₉H₁₆O₆: C, 67.05; H, 4.74. Found: C, 67.06; H, 4.45.

Alkaline Hydrolysis and Cleavage.—The procedure of Hooker and Steyermark⁵ for hydrolysis of 2-methyl-4,5-phthaloylfuran to 2-hydroxy-3-acetonyl-1,4-naphthoquinone (III) was employed for the hydrolysis and cleavage of XI to the same product. A mixture of 0.53 g. of XI and 53 ml. of 1% sodium hydroxide was refluxed until solution

was complete which required 1 hr. The dark red solution was acidified with dilute hydrochloric acid and the mixture allowed to stand overnight. Upon filtration 0.38 g. (79%) of 2-hydroxy-3-acetonyl-1,4-naphthoquinone which melted at 175–176° was obtained. Recrystallization from ethyl acetate-petroleum ether gave a product which melted at 177.0–177.5° (lit.⁸ value 176.5–177.5°) and which had the proper carbon and hydrogen content.

The same product was obtained in 21% yield from XII by the same procedure; it melted at 178–179° both alone and when mixed with the material previously obtained.

When a mixture of 0.15 g. of XIII and 25 ml. of 1% sodium hydroxide was heated under reflux for 24 hr., solution was incomplete and 0.06 g. of unreacted XIII was filtered off. Acidification of the filtrate followed by recrystallization of the resultant precipitate from ethanol-water and then from benzene gave 0.01 g. of light yellow needles which melted at 182.5–183.5° which is the reported⁸ melting point of the expected 2-hydroxy-3-phenacyl-1,4-naphthoquinone.

The identity of the 2-hydroxy-3-acetonyl-1,4-naphthoquinone (III) was confirmed by converting it, in 66% yield, to 2-methyl[1,2-b]furan-4,5-dione (XVI) as previously described; the long deep red needles melted at the reported temperature of 164.0–164.5°.⁸ This product was in turn converted, in 63% yield, by the previously reported procedure to 2-methyl-4,5-phthaloylfuran (XV) which melted at the reported temperature of 246–247°.⁸

Ultraviolet Absorption Spectra.¹⁴—The spectra were determined with a Cary model 14 recording spectrophotometer over the range 215 to 500 m μ using 1-cm. cells. All determinations were made at 23–26° with spectroscopic grade acetonitrile as the solvent. Results are summarized in Table I.

TABLE I
ULTRAVIOLET ABSORPTION DATA

4,5-Phthaloylfuran	λ_{max} , m μ	log ϵ_{max}
2-Methyl- ^a (XV)	250	4.60
	291	3.83
	335	3.49
	382	3.39
2-Methyl-3-benzoyl- (XII)	250	4.66
	287	3.97
	335	3.58
2-Methyl-3-acetyl- (XI)	375	3.47
	250	4.59
	293	3.87
2-Methyl-3-carbethoxy- (XIV)	335	3.55
	360–377 ^b	3.42
	249	4.53
	291	3.88
	339	3.54
2-Phenyl-3-cyano- (X)	372	3.39
	226	4.07
	249	4.35
	260 ^c	4.25
	297	4.46
2-Phenyl-3-benzoyl- (XIII)	341	3.62
	391	3.58
	259	4.61
	281 ^c	4.47
	409	3.65

^a These data agree closely with those previously reported for this compound and for 2-isopropyl-4,5-phthaloylfuran in reference 10. ^b A plateau rather than a peak. ^c A shoulder rather than a peak.

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