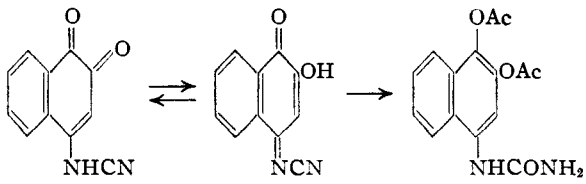
quinone in 60 cc. of alcohol was treated with a solution of 8 cc. of diethylaminoethylamine (prepared by H. H., b. p. 145–147°) in 16 cc. of water and the mixture allowed to stand at room temperature for twenty-four hours with occasional shaking. The clean, dark red solution was allowed to evaporate to dryness on a large watch glass, with the formation of large brown-red crystals. These were washed with chilled 10% methanol and recrystallized from aqueous methanol to give diamond-shaped brick red crystals, 5.7 g. (79%). **2-N-Morpholino-1,4-naphthoquinone** (No. 45) was prepared by heating a solution of 8.4 g. of methoxynaphthoquinone in 280 cc. of alcohol with 10 cc. of morpholine in 20 cc. of water on the steam-bath until a clear claret solution resulted. The solution on standing deposited 9.0 g. (83%) of crystalline product (two crops). Recrystallization from methanol gave long needles of burnt-orange color. **2-β-Hydroxyethylamino-1,4-naphthoquinone**, prepared similarly in 71–85% yield, crystallized from alcohol in bright red needles.

4-Cyanamino-1,2-naphthoquinone (No. 47).[15]—A filtered solution freshly prepared by shaking 14 g. of calcium cyanamide with 100 cc. of water at 25° for three and one-half hours was added to 6 g. of pure potassium 1,2-naphthoquinone-4-sulfonate. A red precipitate separated at once consisting of microcrystalline needles of the calcium salt. Acidification of a suspension of the salt in water gave a yellow substance that crystallized from acetic acid in lustrous golden yellow needles (3.5 g., 81%).

Hydrolysis of the cyanamide derivative with 96% sulfuric acid or with dilute sulfuric or hydrochloric acid proceeded with ease but invariably gave only hydroxynaphthoquinone and not the urea. Treatment with hydrogen chloride in methanol or ethanol gave the corresponding methyl or ethyl ether. However, the urealyl quinone was obtained by hydrolysis of the hydroquinone as follows. A solution of 6 g. of stannous chloride crystals and 15 cc. of 3 *N* hydrochloric acid was added to 2.7 g. of No. 47 suspended in 150 cc. of acetone and the mixture was warmed on the steam-bath until colorless (one hour). The solution was then cooled, filtered, and treated with excess ferric chloride solution and the resulting red precipitate was collected by centrifugation and reprecipitated from sodium carbonate solution. The dried product was an amorphous brick red solid, dec. about 240°, 1.5 g. (51%). For characterization and analysis, the quinone was reductively acetylated at room temperature to the diacetate No. 48, which formed colorless silken needles from aqueous acetic acid.



No. 47 No. 48

(15) Compare the preparation of sulfanilylurea by Winnek, Anderson, Marson, Faith and Roblin, Jr., THIS JOURNAL, **64**, 1682 (1942).

Summary

This paper reports the synthesis of a number of compounds differing from biologically active 2-hydroxy-3-alkyl-1,4-naphthoquinones in various respects, for example, by the replacement of the hydroxyl group by Cl, SH, NH_2, H, or by substitution in the benzenoid ring.

CAMBRIDGE 38, MASS. RECEIVED MAY 13, 1947

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Naphthoquinone Antimalarials. XII. The Hooker Oxidation Reaction[1]

BY LOUIS F. FIESER AND MARY FIESER

Hooker's observations[2] concerning the remarkable reaction in which a 2-hydroxy-3-alkyl or alkenyl-1,4-naphthoquinone is converted into the next lower homolog by the action of alkaline permanganate led him to conclude that the process involves the opening of the quinone ring and a subsequent closing in a different manner. The inference that the hydroxyl and alkyl groups change place in the course of the oxidation was established in experiments utilizing a marking substituent,[3] but the nature of the reaction has not been elucidated further.

We have now found that colorless intermediates can be produced in high yield by the action of hydrogen peroxide–sodium carbonate under conditions previously found suitable for the conversion of 2-alkyl-1,4-naphthoquinones into their oxides[4] and of 2-hydroxy-1,4-naphthoquinone into the 2,3-dihydroxy derivative.[5] The intermediates are crystalline, rather high-melting acidic substances that are very much more soluble in water than the quinones from which they are derived. They are convertible into the lower hydroxyquinone homologs by oxidation with permanganate in alkaline solution, and a substance identical with the hydrogen peroxide product from lapachol has been isolated from a permanganate oxidation of lapachol conducted according to Hooker.

The analyses of several of the colorless intermediates and their derivatives show that the composition is that of the starting quinone plus the elements of hydrogen peroxide. The ketol–keto acid formula II[6] is consistent with the analytical

(1) Work on this problem was conducted intermittently since April, 1940. The experimentation pertaining to the elucidation of structure of the ketol intermediates was carried out by one of us (M. F.) and that concerned with the development of an improved method for the preparation of naphthoquinone antimalarials done by the other.

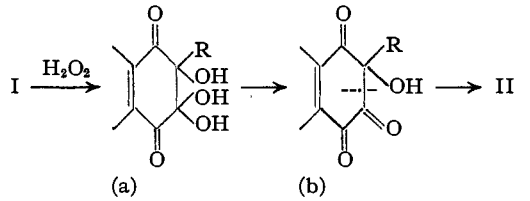
(2) Hooker, THIS JOURNAL, **58**, 1163, 1174, 1179 (1936).

(3) Fieser, Hartwell and Seligman, *ibid.*, **58**, 1223 (1936).

(4) Fieser, Campbell, Fry and Gates, *ibid.*, **61**, 3216 (1939); Tishler, Fieser and Wendler, *ibid.*, **62**, 2866 (1940).

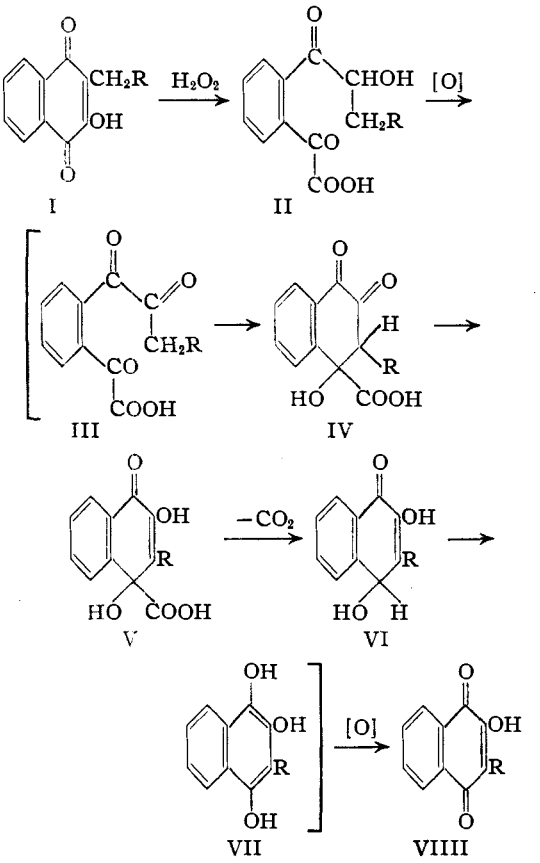
(5) Fieser and Gates, *ibid.*, **63**, 2948 (1941).

(6) One possible route to II is by a β-diketone cleavage:



Dr. H. Heymann has suggested that the intermediate (a) or its ion may undergo a benzilic acid rearrangement to the structure XI below.

data and affords a rational interpretation of the course of the alkaline oxidation: initial oxidation of the ketol group (III) activates the adjacent

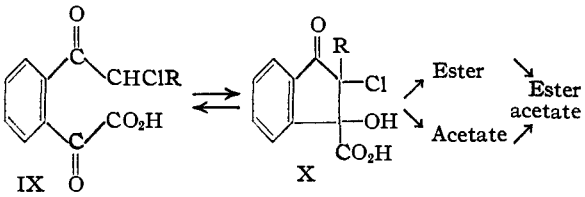


methylene group and promotes aldolization to a cyclic product (IV) that can enolize to a structure (V) subject to ready decarboxylation because it is the vinylog of a β-keto acid. The decarboxylation may be promoted also by the tendency of the product (VI) to undergo aromatization to a hydroquinone (VII) that is subject to ready oxidation to a hydroxyalkylnaphthoquinone (VIII).

Although Formula II accounts for the course of the Hooker oxidation and probably represents one tautomer of the reacting molecule, the ketol is evidently capable of existing in another form or forms because three, rather than two, hydroxylic–carboxylic functions can be characterized. Thus the ketol from lapachol forms, among other derivatives isolated, a methyl ester, an acetate, a dibenzoate and a dibenzoate methyl ester. The derivatives are slow to crystallize, tend to form solvate complexes, and are in general so difficult to isolate that only a positive result is significant; for example, two of the ketols gave only monoacetates, but a third gave a diacetate. The isolation of two dibenzoate methyl esters, and of two other dibenzoates that are acidic but afforded no crystalline esters, definitely establishes the presence of three hydroxylic groups. The problem of formulation is clarified by the characterization of a parallel series of compounds obtained by the reaction of the hydroxyalkylnaphthoquinones as sodium salts with sodium hypochlorite. The colorless products are designated ketol chlorides because they differ from the ketols merely by the presence of chlorine in place of the hydroxyl group and because on alkaline oxidation they afford (in low yield) the same quinone homologs that are obtained from the ketols. Acylation and esterification experiments have revealed the presence in the ketol chlorides of two hydroxylic functions, whereas a formulation corresponding to II would indicate only one such group.

In ultraviolet absorption characteristics the ketols and ketol chlorides are closely related to one another and to acetophenone (and benzoin) and show no resemblance to a model compound containing di-ortho carbonyl substituents (2-methyl-1,4-naphthoquinone oxide). An enediol formulation for the ketols seems to be ruled out both by the spectrographic evidence and by the existence of the parallel series of analogous ketol chlorides; formulations involving an isomerization of the enediol to a β-keto-α-hydroxy structure are excluded on the same grounds. An acetal formulation for the ketols would account for the presence of only two of the three hydroxylic functions that have been characterized. A lactolization between the carboxyl and the ketol carbonyl groups would not increase the number of characterizable hydroxyl groups but might be considered for the formulation of some of the ester derivatives were it not for the observation that the same esters are produced by the action of diazomethane as are formed on Fischer esterification; Newman and McCleary[7] have shown that comparable lactol (pseudo) esters are sometimes formed on Fischer esterification but that diazomethane affords only normal esters.

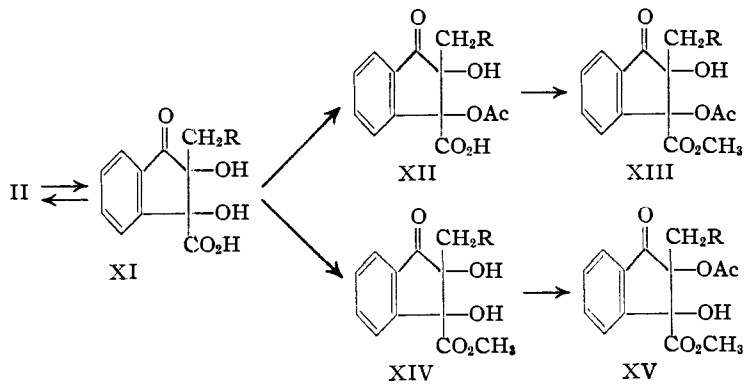
The only plausible explanation that can be advanced is that both the ketols and their chlorides exist largely as cyclic products of aldolization, for example X. The chloride derived from hydro-



lapachol forms a methyl ester (diazomethane) and an acetate (acetic anhydride–zinc chloride) that are convertible into the same methyl ester acetate, and all three derivatives, like the parent compound, have similar spectra indicative of the presence of one carbonyl group conjugated with the benzene ring. The spectrographic evidence indicates that all the derivatives of the ketols are also monocarbonyl derivatives, and two of the ketols

(7) Newman and McCleary, THIS JOURNAL, 63, 1537 (1941).

have been found to afford monosemicarbazones. An interesting deviation from the behavior of the chlorides is that in two instances a given ketol on acetylation and esterification gave a methyl ester acetate isomeric with the product obtained by esterification and acetylation. The cyclic structure XI contains two tertiary hydroxyl groups, corresponding to the formation of several dibenzoates and of one diacetate, but usually one of these groups responds preferentially to acetylation in the cold in the presence of pyridine. Acetylation of the ester requires more vigorous treatment (acetic anhydride–zinc chloride) and apparently results in a preferential attack of the alternate hydroxyl group, and a possible explanation is that the ester group exerts more hindrance to the reaction of the neighboring hydroxyl than does a free carboxyl group. The isomeric ester acetates are thus tentatively regarded as having the structures XIII and XV.



The observation that ketol intermediates in the Hooker reaction can be produced by the hydrogen peroxide method in yields that in some instances are several times as high as the over-all yield of the lower quinone homolog obtainable by any of the modifications of Hooker's permanganate oxidation procedure prompted an investigation of the oxidative ring closure reaction. Successive improvements were made and the following procedure developed: a hydroxyalkylnaphthoquinone is treated with hydrogen peroxide in dioxane–soda solution in a nitrogen atmosphere, the resulting colorless solution of the ketol is acidified and the excess hydrogen peroxide is destroyed with sulfur dioxide, the excess sulfur dioxide is removed in a stream of nitrogen, and the ketol is oxidized with copper sulfate in alkaline solution. In several instances recrystallized products of high purity have been obtained by this procedure in yields of 85–90%. The new procedure has the following advantages over the permanganate reaction: generally higher yields, particularly of unsaturated quinones; no limitation in applicability to quinones of high molecular weight and low solubility in aqueous alkali; no limitation with respect to the size of the sample oxidized.

Experimental

Preparation of Ketols.—The following procedure has been found applicable to quinones of molecular weight ranging from 244 (hydrolapachol) to 384 (M-2309). A 0.01-mole portion of the quinone is dissolved in 25 cc. of dioxane, by slight warming if necessary, and a solution of 1.2 g. of sodium carbonate in 25 cc. of water is added.[8] The resulting red solution or suspension of the sodium salt is heated in a water-bath maintained at 70°, the air is largely displaced by passing in a slow stream of nitrogen over the surface of the liquid, and 2 cc. of 30% hydrogen peroxide solution is added. Heating under nitrogen at 70° is continued until the solution becomes completely or very nearly colorless, which usually requires from twenty to forty minutes. The persistence of a strong red color for a much longer period may be an indication that the quinone sample contained impurities or that the hydrogen peroxide had deteriorated, and hence that more of the reagent should be added. The fully decolorized solution is cooled, diluted with one to two times its volume of water, and made strongly acid with 36% hydrochloric acid (25 cc. for a substance of low molecular weight). A ketol of low molecular weight often separates only after a delay of several minutes, even when the solution is cooled in ice; the higher ketols usually separate as oils that solidify only after a period of one or more hours even when cooled well and scratched. The colorless solid is often found to be in a hydrated condition, as illustrated in Table I.

In early experiments an attempt was made to force the reaction to completion by heating the mixture on the steam-bath and adding several fresh portions of hydrogen peroxide, but a strong pink or even red color persisted and could not be discharged. It was then realized that the reagent decomposes rapidly in this mixture at a temperature as high as 90° but is reasonably stable at 70°, at which temperature no large excess is required. The use of a protective atmosphere of nitrogen was suggested by the observation that an initially colorless solution of a pure ketol in sodium carbonate solution slowly acquires a pink or red color when warmed and exposed to air; it is surprising that, in a nitrogen atmosphere, the excess hydrogen peroxide present does not oxidize the sensitive ketol as air does. The quinone employed should be of high purity, for particulate or other extraneous matter present may catalyze the decomposition of hydrogen peroxide. Thus a batch of hydrolapachol prepared by catalytic hydrogenation of lapachol and crystallized to a satisfactory melting point (94–95°) reacted only poorly and the solution reached a terminal light pink stage only after the addition of fresh hydrogen peroxide and in about two hours. The starting material was then processed in a manner calculated to remove any trace of platinum catalyst by precipitation from a filtered alkaline solution and crystallization from diluted methanol solution after charcoal treatment, and the reaction mixture of the purified quinone (same m. p.) became completely colorless after eleven minutes.

The ketol from hydrolapachol separated on acidification, after a delay of several minutes, as a mass of colorless needles. The material dried to constant weight at 25° proved to be a hydrate; when heated very slowly in a capillary tube it shriveled slightly at 100–110° but melted to a clear liquid only at 169°, and when introduced to a bath at 108° it melted at once with bubbling, solidified, and remelted at 167–168°. Samples (225 mg.) dried to constant weight at 85–90°, lost an amount of water (45, 43 mg.) corresponding to an original tetrahydrate, and the anhydrous material did not melt when introduced to

(8) In case a larger volume of dioxane is required, an equal volume of water containing 1.2 g. of soda is employed.

TABLE I

KETOLS AND CHLORIDES II ⇄ XI

No.	Compound or derivative. $-CH_2R$	Formula	M. p., °C.	Yield, % or method	Solvent	Notes	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
				Ketols						
1	$-CH_2CH{=}C(CH_3)_2$ (Lapachol)	$C_{15}H_{18}O_5$	156–157	70–79	Ether–PE	Small need.	65.20[a]	64.91	5.84	6.12
2	Methyl ester	$C_{16}H_{18}O_5$	156	CH_2N_2; MeOH–HCl	Aq. MeOH	Prisms	66.19	65.99	6.25	6.60
3	Acetate	$C_{18}H_{20}O_6$	98	Ac_2O–$ZnCl_2$		Prisms	65.04	64.84	6.07	6.18
4	Acetate	$C_{17}H_{18}O_6$	157–158	Ac_2O–Py	Ether–PE	Fine need.	64.13	64.46	5.70	6.18
5	Methyl ester	$C_{18}H_{20}O_6$	109–110	CH_2N_2	Ether–PE	Stout need.	65.05	65.14	6.07	6.26
6	Dibenzoate	$C_{29}H_{24}O_7$	172, dec.	C_6H_5COCl, Py	Ether–PE	Needles	71.87	71.80	5.00	5.41
7	Dibenzoate·CH_3OH	$C_{30}H_{28}O_8$	101	Dried at 25°	MeOH	Loses MeOH	69.76	70.23	5.46	5.54
8	Methyl ester	$C_{20}H_{20}O_7$	130–131	CH_2N_2	MeOH	Prisms	72.27	72.59	5.26	5.50
9	Semicarbazone	$C_{16}H_{19}O_5N_3$	195–196, dec.	In EtOH	EtOH	Plates	57.64	57.80	5.75	5.96
10	$-CH_2CH_2CH(CH_3)_2$[b]	$C_{15}H_{18}O_5$	169–170	84–88	Ether–PE	Needles	64.73	65.00	6.52	6.64
11	Monohydrate	$C_{15}H_{20}O_6$	111		Water	Needles	60.80	60.99	6.80	6.98
12	Methyl ester	$C_{16}H_{20}O_5$	119	CH_2N_2	Aq. MeOH	Needles	65.74	66.03	6.90	6.98
13	Dibenzoate	$C_{29}H_{26}O_7$	164	C_6H_5COCl, Py	MeOH	Plates	71.61	71.44	5.39	5.33
14	Methyl ester	$C_{20}H_{28}O_7$	121–122	CH_2N_2	Ether	Microcryst.	71.98	72.25	5.64	5.71
15	$-CH_3$ (Phthiocol)	$C_{11}H_{10}O_5$	229–230	58	C_6H_6	Needles	59.45[c]	59.83	4.53	4.70
16	Monohydrate	$C_{11}H_{12}O_6$	230, dec.		Water	Needles	54.99	55.01	5.04	5.34
17	Methyl ester	$C_{12}H_{12}O_5$	131		Ether–PE	Needles	61.00	61.06	5.14	5.35
18	Acetate	$C_{14}H_{14}O_6$	148–149		Ether	Prisms	60.42	60.64	5.07	5.20
19	Dibenzoate	$C_{25}H_{18}O_7$	185, dec.		MeOH	Stout need.	69.75	69.97	4.22	4.49
20	Methyl ester	$C_{14}H_{14}O_6$	131.5		Ether–PE	Prisms	60.42	60.25	5.07	5.09
21	$-CH_2CH_2CH_2$·Cyclohexyl	$C_{12}H_{24}O_5$	204–205, dec.	93–95	Aq. MeOH	Needles	68.66	68.73	7.28	7.28
22	Methyl ester	$C_{20}H_{26}O_5$	106–107	MeOH–BF_3; CH_2N_2	Lig.; MeOH	Needles	69.34	69.45	7.57	7.75
23	Dibenzoate	$C_{33}H_{32}O_7$	180, dec.	ArCOCl, Py	C_6H_6–Lig.	Prisms	73.31	73.76	5.97	6.22
24	Diacetate	$C_{28}H_{28}O_7$	149.5	Py, Ac_2O	Ether–PE	Prisms	66.33	66.07	6.78	6.95
25	Semicarbazone	$C_{20}H_{27}O_5N_3$	159–160, dec.		EtOH	Needles	N, 10.79	10.36		
26	Methyl ester	$C_{21}H_{29}O_6N_3$	205	CH_2N_2	Aq. MeOH	Plates	62.51	62.62	7.25	7.03
27	$-$Cyclohexyl	$C_{16}H_{18}O_5$	190–191	80.5	EtOAc–Lig.	Micro need.	66.19	66.30	6.25	6.35
28	$-\beta$-Naphthyl	$C_{20}H_{14}O_5$	190–200, dec.		C_6H_6	Needles	71.85	71.89	4.22	4.60
29	$-(CH_2)_4$·Cyclohexyl	$C_{20}H_{26}O_5$	150–151		C_6H_6–Lig.	Micro plates	69.34	69.29	7.57	7.57
30	$-(CH_2)_2CHMe(CH_2)_3CHMe_2$[d]	$C_{20}H_{28}O_5$	131–133	60.5	C_6H_6–Lig.		68.92	68.86	8.09	8.38
31	$-(CH_2)_3C_6H_4OC_6H_5$-p	$C_{25}H_{22}O_6$	142–143		C_6H_6	Micro need.	71.76	72.04	5.30	5.49
				Chlorides						
32	$-CH_2CH_2CH(CH_3)_2$	$C_{15}H_{17}O_4Cl$	134–135		C_6H_6–Lig.	Plates	60.71	60.90	5.78	5.85
33	Methyl ester	$C_{16}H_{19}O_4Cl$	102–103	CH_2N_2	Ether–PE	Prisms	61.83	61.66	6.16	6.52
34	Acetate	$C_{17}H_{19}O_5Cl$	165–166	Ac_2O, Py	Ether–PE	Prisms	60.27	60.42	5.65	5.75
35	Methyl ester acetate	$C_{18}H_{21}O_5Cl$	85.5–86		Ether–PE	Plates	61.28	60.89	6.15	6.13
36	$-CH_2CH_2CH_2$·Cyclohexyl	$C_{19}H_{23}O_4Cl$	172–173	96	C_6H_6	Prisms	65.04	65.41	6.61	6.84
37	Methyl ester	$C_{20}H_{25}O_4Cl$	116–117	CH_2N_2	Aq. MeOH	Plates	65.83	65.89	6.91	7.01
38	Acetate	$C_{21}H_{25}O_5Cl$	166, dec.	Ac_2O, Py	Pet. ether	Prisms	64.20	64.50	6.41	6.73
39	Benzoate	$C_{26}H_{27}O_5Cl$	184	C_6H_5COCl, Py	Aq. MeOH	Plates	68.64	68.81	5.98	6.31
40	Methyl ester	$C_{27}H_{29}O_5Cl$	137	CH_2N_2	Ether–PE	Plates	69.15	69.00	6.22	6.33
41	$-CH(C_6H_5)_2$·Etherate	$C_{27}H_{27}O_5Cl$	194		Ether–PE	Prisms	69.45	69.78	5.83	6.13
42	Methyl ester	$C_{24}H_{19}O_4Cl$	165–166	CH_2N_2	Ether–PE	Needles	70.84[e]	70.83	4.71	4.86

[a] Neut. equiv. calcd., 276; found, 287. [b] First sample prepared by W. G. Dauben. [c] Neut. equiv. calcd., 222; found 224. [d] Prepared by W. G. Dauben. [e] Calcd.: Cl, 8.72; found Cl, 8.74.

a hot bath. The yield of anhydrous material was 84%; when the reaction was conducted in water alone, without dioxane, the yield was 88%. The two figures for the yield of the ketol from lapachol similarly refer to experiments conducted in the presence and absence of dioxane; the product crystallized from the acidified solution (five-minute delay) in an anhydrous condition, m. p. 150–152°.

The ketol from phthiocol is considerably more soluble than the others and even when no dioxane was used the yield of product that separated slowly in dense white crystals was only 58%. The crude product was anhydrous and melted at 217–219°, dec. The substance gives a positive iodoform test. The ketol from M-1916 separated on acidification as a solid, which when dried at 90° was anhydrous and melted at 198°. The substance is much less soluble in hydroxylic solvents than the above ketols and can be crystallized from a very slightly diluted methanol solution as large, heavy needles of unsolvated product. The ketol from M-2309 separated as an oil that only slowly solidified. The air-dried solid melted at about 105°, weighed 14% more than the theoretical for anhydrous product, and gave off water when heated with benzene. The yield of pure product that crystallized from the benzene solution was only 61%, but since ketol prepared in the same way but not isolated afforded the lower quinone homolog in 91% yield it is concluded that the amount of pure ketol isolated by crystallization is not indicative of the true yield. Similar observations were made in the other instances where no yield is reported. We think it likely that the oxidation proceeds quantitatively in all instances and that apparent losses are due to idiosyncrasies of the compounds or to stereoisomerism.

Preparation of Ketol Chlorides.—A warm solution of 1.49 g. (0.005 mole) of M-1916 in 20 cc. of dioxane was treated with a solution of 0.6 g. of sodium carbonate in 37.5 cc. of water and the mixture boiled until the red salt was all in solution. The red solution deposited no solid when cooled in ice; commercial sodium hypochlorite was then run in from a burette and the solution titrated to a point where it was very nearly colorless (delay of a minute or two at the end). On acidification the product separated as an oil that changed in a few minutes to a granular white solid. When dried at 90° the product was found to be anhydrous and melted at about 160° (yield 96%). Crys-

TABLE II

ULTRAVIOLET ABSORPTION SPECTRA IN ABSOLUTE ETHANOL

Compound	Absorption maxima (or inflections), wave lengths in mμ, log E values			
Model Compounds				
2-Methyl-1,4-naphthoquinone oxide	227.5, 4.4	265, 3.7	302, 3.3 310, 3.27	340, 2.3
Acetophenone[a]	240, 4.12	278, 3.02		320, 1.70
Benzoin (in hexane)[b]	243, 4.0	283, 3.1	294, 2.9	320, 2.56
Desyl chloride (in hexane)[c]	240, 4.0	281, 2.94	290, 2.75	332, 2.2
Ketol from Lapachol				
Ketol	243, 4.0		287.5, 3.2	330, 2.2
Methyl ester	244, 4.0		287.5, 3.2	327, 2.2
Acetate	(242.5), 4.0		282.5, 3.3	322, 2.1
Acetate of ester (98°)	245, 4.0		282.5, 3.2	325, 2.2
Ester of acetate (110°)	245, 4.0		277, 3.2	325, 2.1
Dibenzoate	232.5, 4.5	(248), 4.2	281, 3.5	327, 2.0
Dibenzoate methyl ester	235, 4.5		281, 3.5	322, 2.1
Semicarbazone	236, 3.8 228, 3.8	283, 4.0	302.5, 4.04	310, 3.95
Ketol Chloride from M-1916				
Ketol chloride	246.5, 4.03		290, 3.3	322, 2.1
Methyl ester	245, 4.02		285, 3.3	325, 2.0
Acetate	250, 4.05		285, 3.1	327, 1.8
Benzoate	234, 4.3		282.5, 3.4	322.5, 2.1
Benzoate methyl ester	236, 4.3	(260), 4.0	281, 3.4	327, 1.9

[a] Ley and Wingchen, *Ber.*, **67**, 501 (1934). [b] Castille, *Bull. Acad. Roy. Belg.*, **12**, 498 (1926). [c] Preiswerk, *Helv. Phys. Acta*, **7**, 203 (1934).

tallization from slightly diluted methanol gave well formed prismatic needles (melts with bubbling in a bath at 120°, solidifies, and remelts at 169–171°). This loses some 7% of solvent when dried at 90° to give anhydrous material in 81% yield. The substance also crystallizes satisfactorily from benzene.

Treatment of hydrolapachol with hypochlorite in the same way gives a crude product that corresponds in weight to close to the theoretical amount but is sticky and low melting. Crystallization from benzene is tedious and affords pure material in only about 50% yield and the residual material is a glass. It is not known whether this contains a substantial amount of the ketol chloride, perhaps in another cyclic form, or some other product. The pure chloride and the total crude product both gave about the same yield of quinone when submitted to the second oxidation procedure described below, but the yield was in each case very low.

Isolation of a Ketol from a Hooker Oxidation.—A 2-g. sample of lapachol was oxidized with alkaline permanganate at 0° in the exact manner prescribed by Hooker.[2] The manganese dioxide was removed by filtration after twenty minutes, the solution was acidified, and the orange precipitate of quinone collected. The aqueous liquor was then extracted with ether and the dried extract evaporated almost to dryness. On cooling and scratching, a sticky yellowish solid was obtained, and this was rubbed with ether–petroleum ether and then clarified in ether with charcoal and crystallized from ether–petroleum ether. A colorless product was obtained that melted at 151° both alone and when mixed with the ketol obtained by hydrogen peroxide oxidation; yield 0.4 g. The substance further yielded a methyl ester identical with that from the known ketol. No ketol was isolated in a Hooker oxidation utilizing just half the prescribed amount of permanganate; considerable unchanged lapachol was found present.

Preparation of Derivatives.—The esters reported in Table I were usually prepared by the action of diazomethane in ether, but in a few test cases identical esters were obtained by esterification of the ketols with methanol in the presence of either hydrogen chloride or boron fluoride etherate. The **acetylation of a ketol** was conducted by adding 0.5 cc. of acetic anhydride to a solution of 0.5 g. of ketol in 2 cc. of pyridine and allowing the solution to stand for from one to four days at room temperature. Dilution with water gave a clear solution from which the acetate was precipitated as an oil on acidification; the product was collected by ether extraction, and solid material usually was secured most satisfactorily by chilling a solution in ether or ether–petroleum ether in Dry Ice and scratching. The **acetylation of an ester or a ketol chloride** was conducted by adding a small crystal of anhydrous zinc chloride to a suspension of 0.5 g. of the material in 4 cc. of acetic anhydride and shaking the mixture occasionally. After about twelve hours the ester had dissolved, and when water was added and time allowed for hydrolysis the product eventually was obtained as a solid.

Benzoylation was conducted by adding 1 cc. of benzoyl chloride to a solution of 1 g. of ketol or ketol chloride in 3 cc. of pyridine at room temperature. After one to two days water was added and the benzoate separated (without the addition of hydrochloric acid).

The preparation of **semicarbazones** was carried out by adding two equivalents each of semicarbazide hydrochloride and sodium acetate to a solution of 0.5–1 g. of material in 5–10 cc. of alcohol and 1 cc. of water. The solution was refluxed for two to three hours and cooled, and the crystalline product was collected. Ketol methyl esters were recovered unchanged after this treatment.

Ultraviolet Absorption Spectra.[9]—Table II records the results of determinations carried out with a Beckmann spectrophotometer in solutions in absolute ethanol (distilled from magnesium ethoxide); the figures given in the last column locate the approximate center of a broad band. The ketol from lapachol has the same spectral characteristics as its acetate and ester derivatives, differs markedly from methylnaphthoquinone oxide, resembles acetophenone, and shows a still closer analogy to benzoin,

(9) We are indebted to Dr. Eleanor Mitts Behrmann for conducting the spectrographic determinations.

TABLE III

OXIDATION OF PURE KETOLS WITH COPPER SULFATE–SODIUM HYDROXIDE

Ketol from	Side chain	Weight, g.	Product	Crude product M. p., °C.	G.	%	Purest sample, m. p., °C.
Hydrolapachol	$-CH_2CH_2CH(CH_3)_2$	1.39	Norhydrolapachol	134–135	1.00	87	134–135
Lapachol	$-CH_2CH{=}C(CH_3)_2$	2.76	Norlapachol	119–120	1.92	84	121–122 (dil. MeOH)
Phthiocol	$-CH_3$	1.19	Hydroxynaphtho-quinone	193–194	0.78	90	195–196
M-1916	$-(CH_2)_3$-Cyclohexyl	1.66	M-1915	102–104	1.40	(98.5)	111–112 (Needles,
				From MeOH:	1.22	86	MeOH)

which constitutes the best available model for the postulated structure XI. The dibenzoyl derivatives show a displacement of the K band that can be attributed to added absorption by the benzoyl radicals, and hence these substances appear to contain the original carbonyl group of the ketol. The ketol chloride investigated closely resembles the above ketol and the model substance desyl chloride.

All of the compounds investigated, except the ketol dibenzoate and its methyl ester, were found to undergo change in very dilute solution (0.00002 *N*); with the ketol, for example, the bands in the range 235–260 mμ disappeared within three to four hours. The determinations reported were made with solutions of concentrations above 0.0001 *N*, which showed satisfactory stability.

Oxidation of Pure Ketols to Quinones.—In early experiments three of the ketols were oxidized with alkaline permanganate at 0° as in a regular Hooker oxidation. Quinones identical with the products of Hooker oxidation were obtained, but little if any improvement in yield was noted. The first milder alkaline oxidizing agent tried, potassium ferricyanide, gave much better results. Thus a solution was prepared by heating 278 mg. of hydrolapachol ketol and 84 mg. of sodium bicarbonate with 10 cc. of water and to it was added a solution of 1.32 g. of potassium ferricyanide in 5 cc. of water to which 5 cc. of 25% sodium hydroxide was added. The solution was let stand for ten minutes, cooled, and acidified. A yellow product that separated proved to be norhydrolapachol of good quality, m. p. and mixed m. p. 134–135°; yield 202 mg. (76.5%). Although this and other results appeared promising, the reaction products sometimes contained bluish or greenish contaminants and were not as clean as those obtained with a copper salt.

Oxidation with Fehling solution proceeds very well but the material that separates on acidification is a mixture of the quinone and tartaric acid. The mixture so obtained from hydrolapachol ketol was extracted with ether and the solution on evaporation afforded bright yellow norhydrolapachol, m. p. 134–135°, in 78.5% yield. Since the separation constitutes an additional operation, experiments were made to see if the amount of tartaric acid could be substantially reduced, and it was eventually found that this reagent can be omitted altogether. Thus a solution of 1.66 g. (0.005 mole) of M-1916 ketol in 12.5 cc. of dioxane and 12.5 cc. of water containing 0.6 g. of sodium carbonate was treated with 10 cc. of 25% sodium hydroxide solution and 25 cc. of water containing 5 g. of copper sulfate crystals. The supernatant liquor rapidly acquired a red color; the mixture was allowed to stand for ten minutes and then was warmed on the steam-bath for ten minutes and filtered through a pad of Super-Cel and the red salt washed through with methanol and water. The filtrate when acidified deposited a very clean, bright yellow product that on crystallization afforded the homologous quinone M-1915 of high quality in 86% yield. The results summarized in Table III show that in three other instances quinones of high purity were obtained by the same procedure in yields of 84–90%. A suspension of sulfur in alkali also oxidizes the ketols to quinones, but no easy method was found for separating the reaction product from the sulfur that precipitates with it on acidification.

Two-Step Hooker Oxidation: First Procedure.—The results of the exploratory oxidations recorded in Table IV were obtained by the following procedure. A 0.01-mole sample of a quinone was treated with excess hydrogen peroxide in dioxane–soda solution exactly as described above and the resulting colorless solution of the ketol was treated with 1 cc. of the copper sulfate solution described below to decompose the excess hydrogen peroxide. When the vigorous gas evolution ceased, the solution was heated on the steam-bath for ten minutes with 10–20 cc. of 25% sodium hydroxide and 50 cc. of a solution containing 10 g. of copper sulfate crystals. The resulting red solution was filtered and acidified as above and the precipitated quinone collected and dried to constant weight. The first few quinones listed in the table are of low molecular weight and the precipitated, bright yellow products were of such high purity that the yield of crude product provides a fair measure of the course of the reaction. In these instances the yields are good, but not as high as obtained by oxidation of the pure ketols by the same method (Table III). In the case of the quinones of higher molecular weight the yield of crude, precipitated material was often close to the theoretical amount but the melting point was some 10–15° below that of the pure product. One crystallization raised the melting point to a value satisfactory for calculation of the yield, but the yield of such material was in the range 40–65%. Comparisons made with both hydrolapachol and M-1916 showed that a better over-all yield can be obtained by isolating the pure ketol and oxidizing it than by conducting the two processes in the same solution. The processing of the mother liquor of the two-step oxidation of M-380 to M-2293 revealed the presence of *trans*-4′-cyclohexylcyclohexanecarboxylic acid (m. p. 156–159°; no depression in mixed m. p.); the formation of an acid by-product accounts for at least some of the loss in yield and explains why quinones of high molecular weight are precipitated in a contaminated condition whereas the lower members are not (acid by-product soluble in water). A trial was made to see if the acid might arise from the action of excess hydrogen peroxide, but when 0.50 g. of pure M-1916 ketol was heated in dioxane–soda solution with 5 cc. of 30% hydrogen peroxide for three hours at 70° 0.48 g. of pure ketol was recovered. A suspicion that oxidation to the acid occurs in the process of decomposing the excess hydrogen peroxide under the catalytic influence of cupric ion was then confirmed by experiment; pure M-1916 ketol was badly damaged by treatment in dioxane–soda with a large amount of hydrogen peroxide in the presence of copper sulfate, for an inferior, sticky product was recovered in low yield. The procedure was then modified to provide for the destruction of the excess hydrogen peroxide by reduction, rather than gassing, as described in the next section.

Final Procedure.—A 0.01-mole sample of a quinone in 25 cc. of dioxane and 25 cc. of water containing 1.2 g. of sodium carbonate was heated with 2 cc. of 30% hydrogen peroxide under nitrogen at 70° until the solution was colorless. The ketol solution was then cooled in ice and treated with 2 cc. of 36% hydrochloric acid and with a sufficient amount of water saturated with sulfur dioxide to give an excess recognizable by odor (about 12 cc.). A stream of nitrogen was then bubbled into the suspension of oily or solid ketol until the excess sulfur dioxide had been eliminated (odor, one to two hours). The mixture was then treated with 20 cc. of 25% sodium hydroxide and 50 cc. of a solution containing 10 g. of copper sulfate

TABLE IV

TWO-STEP HOOKER OXIDATION; FIRST PROCEDURE

Quinone oxidized	Side chain	Weight, g.	Product	Crude product M. p., °C.	Crude product G.	Crude product %	Once cryst. prod. M. p., °C.	Once cryst. prod. %	Purest sample M. p., °C.
Hydrolapachol	$-CH_2CH_2CH(CH_3)_2$	2.44	M-1706	134–135	1.70	74			134–135
M-1706	$-CH_2CH(CH_3)_2$	5.88	M-264	89–90	4.20	76.5			92–93
Lapachol	$-CH_2CH=C(CH_3)_2$	2.42	Norlapachol	119–120	1.44	63	119–120		121–122
M-2287	$-(CH_2)_6CH(CH_3)_2$	1.66	M-300	74–75	1.25	(79)			81.5–82.5 (fine needles)
M-2256	$-C_{17}H_{35}$-*n*	2.06	M-2348	92–93	1.85		100–101	49	100–101 (micro needles)
M-1714	$-C_{16}H_{31}$-*n*	3.84	M-2347	84–86	3.27		95.5–97	38	96.5–97.5 (micro needles)
M-380	$-CH_2C_6H_{10}$-C_6H_{11}-*trans*	3.40	M-2293	177–180	2.75		195–196	60.5	195–196 (needles from HOAc)
M-2321	$-(CH_2)_2$-Cyclopentyl	2.86	M-1920	134–142	2.38		158–160	57	159–160 (prisms from MeOH)
M-1920	$-CH_2$-Cyclopentyl	1.54	M-2326		0.90		99–100	44	99–100 (needles, dil. MeOH)
M-2291	$-(CH_2)_2$-$C_6H_{10}C_6H_{11}$-*cis*	1.90	M-2329				150–151.5	67	150.5–151.5 (prisms, EtOH)
M-1916	$-(CH_2)_2$-Cyclohexyl	1.49	M-1915	102–104	1.12	(79)			111–112

crystals and either heated for ten to thirty minutes on the steam-bath or let stand for one or two hours; the conditions in this step are varied in accordance with the nature of the substance being oxidized and the rapidity with which the characteristic red color develops. When the molecular weight of the product is high, the sodium salt separates as a red oil, and in this case it is advisable to add enough dioxane to bring the salt into solution before filtration. The solution is filtered by suction through a pad of Super-Cel and the filter pad is washed with water or dioxane as required until the washings come through colorless. The red solution is then acidified and cooled in ice, preferably for several hours (even a quinone of fairly high melting point may separate initially as an oil or a sticky solid and then change, on standing, to a hard, granular solid).

Results obtained by this improved procedure are recorded in Table V; analyses of new quinones listed in this or a subsequent table are reported in Papers IV-XI. The yields in the oxidation of M-1916 and lapachol are distinctly better than obtained by the first procedure and are as good as or better than when the pure ketol is isolated. The yield from lapachol (76%) is over twice that obtained by Hooker with the use of potassium permanganate. The high yields in the first four oxidations listed illustrate the usefulness of the new procedure for application to higher members of the series that are particularly difficult to oxidize by the Hooker procedure because of their sparing solubility. The smooth oxidation of M-2309 in 91% yield is particularly striking because Dr. Berliner, in preparing a sufficient amount of the product M-2338 for assay, had first oxidized four 1–2 g. samples with irregular results (highest yield 15.6%) and then oxidized four 0.5-g. samples with an average yield of 20.8%.

2-Hydroxy-3-ω-phenylalkyl-1,4-naphthoquinones.—The yields in the last four oxidations of Table V are somewhat uncertain because of peculiarities of members of this series in melting point characteristics and behavior on crystallization. The starting material, the ω-phenylnonyl derivative M-2301, had been prepared by Dr. Berliner, who crystallized the quinone from 90–120° ligroin and initially found the melting point 65.5–66.6° for a sample of the correct analysis (C, 79.47; H, 7.53), but later obtained other preparations of slightly higher melting point. He noted that the compound does not form well-defined crystals and tends to separate as an oil. In the present work one of Berliner's samples was first washed with bicarbonate in ligroin solution and the recovered material crystallized from aqueous methanol containing a little hydrochloric acid to discharge a reddish color, but the product was obtained partly as a solidified oil. On recrystallization from 30–60° ligroin the substance was deposited in a hard crystal cake, m. p. 78–79°. Slow crystallization from a sufficiently large volume of aqueous methanol to prevent oiling gave small, ill-defined crystal aggregates of the same melting point, but remelting in a camphor-like manner. The sample was then extracted from ligroin with alkaline 90% methanol and the material recovered in ether and the sodium salt largely distributed into the ether phase by shaking it with water containing a small amount of alkali. The quinone was then recovered and crystallized finally from 30–60° ligroin, when it was deposited as small balls seen under the microscope to consist of dense cones of very small needles. The melting point was still 78–79°; the analysis of this sample is reported in Paper VIII. Thus the preparations melting at approximately 67° and 79° both gave satisfactory analyses, and furthermore they were found to have exactly the same antirespiratory activity. The difference is therefore attributable to polymorphism.

The highly purified sample, m. p. 79°, was used for oxidation to M-2382, and this after one crystallization softened at 82° and melted, camphor-like, at 86°. The material was put through the double extraction process applied to M-2301 and then crystallized from 60–90° ligroin, from which it separated in excellent, bright yellow needles; these softened at 81°, melted camphor-like at 88°, and behaved the same after solidification. Another

TABLE V

TWO-STEP HOOKER OXIDATION; FINAL PROCEDURE

Quinone oxidized	Side chain	Weight, g.	Product	Crude product M. p., °C.	Crude product g.	Crude product %	Once cryst. product M. p., °C.	Once cryst. product G.	Once cryst. product %	Purest sample M. p., °C.
M-1916	$-(CH_2)_2$-Cyclohexyl	2.98	M-1915	102–104	2.62	(93)	111–112	1.87		111–112
							108.5–110	0.46	82	
M-1971	$-(CH_2)_4$-Cyclohexyl	3.12	M-1916	125–127	2.90		131–132	2.22		131–132
							131–132	0.14	86	
M-2309	$-(CH_2)_2C_6H_4OC_6H_5$-*p*	3.84	M-2338	125–126.5	3.69		128–129	3.14		128–129 (Needles, lig.)
							127.5–128.5	0.25	91	
M-2338	$-(CH_2)_2C_6H_4OC_6H_5$-*p*	2.25	M-2380	156–158	2.11		162–163	1.69		162–163 (Plates, EtOH)
							161.5–162.5	0.20	87.5	
Lapachol	$-CH_2CH=C(CH_3)_2$	2.42	Norlapachol	118–119	1.73	76	120–121	1.53		121–122
M-380	$-CH_2C_6H_{10}$-C_6H_{11}-*trans*	0.170	M-2293	191–192	0.143	(89)	195–196	0.114	70	195–196 (HoAc or EtOH)
M-1714	$-C_{16}H_{31}$-*n*	0.768	M-2347	92–94	0.676	(91)	97–98	0.578	78	97–98
M-2347	$-C_{14}H_{29}$-*n*	0.578	M-1924	80–82	0.512	(92)	89	0.410	74	89
M-2301	$-(CH_2)_9C_6H_5$	2.78	M-2382	79	2.54		86	1.86	72	88 (camphor-like)
M-2382	$-(CH_2)_6C_6H_5$	1.53	M-2386		1.21		83	0.88	60	86–87
M-2386	$-(CH_2)_7C_6H_5$	0.43	M-2387	83	0.34	(83)	89.5	0.21	51	92 (camphor-like)

preparation purified by several crystallizations from aqueous methanol and from ligroin had the same characteristics, and hence it appears that this is an attribute of the pure quinone.

The phenylheptyl derivative M-2386 obtained from the purest M-2382 initially melted over a range to 83°, but one crystallization from ligroin and two from methanol gave beautiful blades of sharp m. p., 86–87°. The next homolog, M-2387, after thorough purification formed large silken needles from 60–90 and 90–120° ligroin, that again melted over a range: softening at 83° and disappearance of the last crystal at 92°.

Because of these peculiarities, a reëxamination was made of the next lower homolog M-2276 (phenylpentyl). Analytically satisfactory samples of this quinone had been prepared independently by C. Heidelberger and F. J. Bondhus, who observed the melting points 86–87° and 96.5–100°. A sample prepared by Miss Bondhus was crystallized several times as follows with the melting points indicated: methanol, 93–95.5°; 60–90° ligroin (small amount required), 101–102° (needles); 60–90° ligroin (three times the volume required before), 105–106°; 90–120° lig., 110–111°; recryst., 112.5–113.5° (granules), 116–117° (better cryst.), 118–119° (good cryst.); aqueous methanol, 125–126° (mat of needles); recryst. 126–127°; 126.5–127.5°. A fresh sample was refluxed in 90–120° ligroin for six hours and then let crystallize, but the melting point was 97–98°. Processing by the double extraction process also failed to produce any great rise in melting point (101–103°). The peculiar behavior is not understood.

Summary

Treatment of a 2-hydroxy-3-alkyl-1,4-naphthoquinone with hydrogen peroxide in dioxane–soda solution gives a colorless acid that is an intermediate in the Hooker reaction and that can be converted by the action of copper sulfate and alkali into the hydroxynoralkylnaphthoquinone in very high over-all yield. The oxidation of the intermediates is interpreted in terms of a ketol–keto acid formulation (II), but characterization of the intermediate ketols, and of corresponding ketol chlorides obtained by the action of hypochlorous acid, by the formation of derivatives and by spectroscopy indicates that the substances exist largely in a cyclic form (XI).

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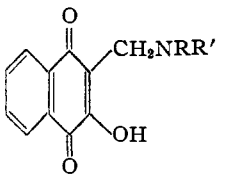
[CONTRIBUTION FROM THE ORGANIC RESEARCH DEPARTMENT OF ABBOTT LABORATORIES]

Naphthoquinone Antimalarials. XIII. 2-Hydroxy-3-substituted-aminomethyl Derivatives by the Mannich Reaction

BY MARLIN T. LEFFLER AND ROBERT J. HATHAWAY

Following the observation[1] that certain 2-hydroxy-3-alkyl-1,4-naphthoquinones possess antimalarial activity against *P. lophurae* in ducks, this series of quinones was extended further by the preparation of other types of derivatives. In the work now being described, the Mannich reaction was used to introduce basic side chains into the *lawsone* (2-hydroxy-1,4-naphthoquinone) molecule. These "Mannich bases" are represented by the general formula I.



(I)

(where R is hydrogen or alkyl and R′ is alkyl, alicyclic or aralkyl; or where —NRR′ makes up a heterocyclic ring)

Although the Mannich reaction with lawsone has not been studied previously, a number of substituted phenols have been shown to condense satisfactorily with formaldehyde and secondary amines.[2] Also, hydroquinone itself was converted to 2,5-dimethylaminomethylhydroquinone by this method.[3] We have found that many amines react unusually well with lawsone and formaldehyde to give beautiful, crystalline solids in high yields. Surprisingly, primary amines, such as butylamine, gave especially good yields (Table I).

A most satisfactory procedure for carrying out the condensation was to employ approximately a one mole ratio of amine, formaldehyde (as formalin) and lawsone in alcohol solution. In this solvent the product of the reaction separates in a relatively pure state. At the start of the reaction, the amine first forms a salt with lawsone; this salt is then converted by formaldehyde into the 2-hydroxy-3-aminomethylnaphthoquinone.

These quinones are highly colored (orange to dark red) compounds and, being amphoteric, they no doubt exist as the "zwitterions." They are indicators in solution. On the alkaline side their solutions are red, while in acid the color is light yellow. It developed that the solubility of these "Mannich bases" in dilute acids proved to be of value in following the course of the reaction during their preparation. Thus in several instances, as noted below, either the Mannich condensation did not take place as expected or the product was to some extent unstable. This could be detected immediately through the lack of complete solubility of the product in dilute hydrochloric acid.

Although most of these substituted quinones were sufficiently stable to be purified by recrystallization, it was observed that several of them were decomposed slightly into an acid-insoluble product by long boiling in alcohol solution. Particu-

(1) Paper I, THIS JOURNAL, **70**, 3151 (1948).

(2) For a recent review of the Mannich reaction, see Blicke, "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., Vol. I, 1942, p. 303.

(3) Caldwell and Thompson, THIS JOURNAL, **61**, 765 (1939).