effect. Rockwood and Husa[2] found that *m*-aminobenzoic acid caused a slight decrease in the activity of urease; a similar result was obtained in the present study with a related amino ester, namely, ethyl 4-hydroxymethyl-3-aminobenzoate.

Effect of Quinine Hydrochloride.—Rona and co-workers[3] have shown that quinine hydrochloride retards the action of certain lipases. A similar result was observed with urease (see Table I).

Effect of Mercurochrome 220 Soluble.—Mercurochrome 220 soluble inactivated urease.

Summary

1. The marked promoter effect of α-amino acids on urease has been verified.
2. Introduction of a methyl group in the alpha position in an α-amino acid does not decrease the promoter effect.
3. δ-Amino-*n*-valeric acid does not have a promoter effect on urease. This is in accord with the previous conclusion that the promoter action is a function of the distance between the amino and carboxyl groups.
4. The enzymic activity of urease was slightly decreased in the presence of quinine hydrochloride or ethyl 4-hydroxymethyl-3-aminobenzoate.
5. Mercurochrome 220 soluble inactivated urease.

GAINESVILLE, FLORIDA

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF BRYN MAWR COLLEGE]

THE ALKYLATION OF HYDROXYNAPHTHOQUINONE
II. CARBON ALKYLATION

BY LOUIS F. FIESER

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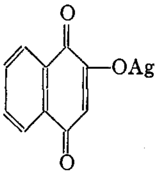
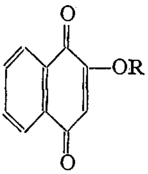
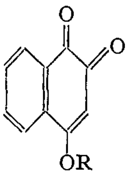
In a previous paper[1] it was shown that isomeric oxygen ethers (II and III) are formed by the action of saturated alkyl halides on the silver salt of hydroxynaphthoquinone (I). Having found that the relative amount of the normal reaction product (II) increases somewhat with increasing reactivity of the alkyl halide, it was to be expected that the very reactive,



I



II



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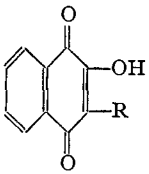

IV

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[3] Rona and others, *Biochem. Z.*, **134**, 108, 118 (1922).

[1] Fieser, THIS JOURNAL, **48**, 2922 (1926). The sub-title of this paper should read "I. Oxygen ethers," instead of "I. Ortho-ethers."

unsaturated halides would give still more of II and less of III than are formed in the reaction with methyl iodide.

It has been found, however, that the reaction in this case follows still a third course. Allyl bromide reacts with the silver salt in question to give in addition to the two O-ethers an acidic isomer which, as shown below, is 2-allyl-3-hydroxy-1,4-naphthoquinone (IV, R = $-CH_2CH{=}CH_2$). Since neither of the O-ethers undergo rearrangement under the conditions of the experiment, the allyl-hydroxynaphthoquinone must be the product of direct C alkylation. It was also found that C-alkyl derivatives are formed in varying amounts in the reaction of the silver salt of hydroxynaphthoquinone with cinnamyl, benzyl, diphenylmethyl and triphenylmethyl halides.

The yields obtained in a series of comparable experiments are given in Table I. The reaction, which was carried out in benzene solution usually at room temperature, was not equally smooth in all cases. For example, while the allylation products were easily separated and purified, considerable oily material which could not be identified was produced in the reaction with cinnamyl chloride and a complete account of the course of the reaction is thus lacking.

Table I

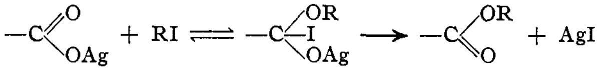
Percentage Yields of Alkylation Products

Alkyl halide	*p*-Quinone ether (II) %	*o*-Quinone ether (III) %	C-Alkyl deriv. (IV) %
$C_2H_5I^a$	13	80	..
$C_2H_5Br^a$	4	88	..
CH_3I^a	26	70	..
$CH_2{=}CHCH_2I$	17	32	21
$CH_2{=}CHCH_2Br$	6	64	17
$C_6H_5CH{=}CHCH_2Cl$	..	..	51
$C_6H_5CH_2Br$	8	51	23
$(C_6H_5)_2CHBr$	58	..	23
$(C_6H_5)_3CCl$	..	..	84

[a] These results, included for the purpose of comparison, are taken from an earlier paper, Ref. 1.

Reasons have been given[1] for considering that II is formed by replacement and that III is produced by 1,4 addition with subsequent elimination of silver halide. The third product, the C-alkyl derivative, is in all probability formed by the 1,2 addition of the alkyl halide as in the alkylation of the salts of aceto-acetic ester. According to this interpretation, the relative amounts of the different products formed depend upon the relative rates of three independent, competing reactions, and the values in the table thus furnish some indication of the relative tendency of the various alkyl halides to react by replacement, 1,4 addition, and 1,2 addition. With methyl iodide 1,4 addition is more than twice as fast as replacement and no 1,2 addition product is formed. Still less replacement occurs with ethyl iodide, probably because the replacement reaction is much slower while there is little change in the rate of the addition reaction. Similarly, a bromide gives less replacement than the corresponding iodide. With the unsaturated halides, however, in spite of the high velocity of ordinary metathetical reactions, replacement predominates only in the case of diphenyl-bromomethane. Two types of addition take place and in general a high reactivity of the halide, as judged by the rates of metathetical reactions,[2] appears to favor 1,2 addition. Thus, triphenylchloromethane gives almost exclusively the 1,2 addition product, benzyl bromide yields less of this product, and still a smaller amount is produced with allyl bromide. Allyl iodide gives a higher yield of the 1,2 addition product than is formed with the bromide. On the other hand, diphenylbromomethane appears out of order in comparison with its homologs, and the relative behavior of the cinnamyl and allyl halides would hardly be expected from the fact that allyl bromide adds more rapidly than cinnamyl bromide to pyridine.[3] Undoubtedly many factors, some perhaps specific, determine the relative rates of the three reactions with each particular halide and an adequate interpretation of the process must await the accumulation of further facts.

These results furnish a suggestion concerning the course of the reaction between the silver salts of carboxylic acids and alkyl halides. The reaction may be simple replacement or it may involve addition:



$$-C\begin{matrix}\diagup O\\ \diagdown OAg\end{matrix} + RI \rightleftharpoons -C\begin{matrix}\diagup OR\\ -I\\ \diagdown OAg\end{matrix} \longrightarrow -C\begin{matrix}\diagup OR\\ \diagdown O\end{matrix} + AgI$$

Since in the case of hydroxynaphthoquinone, a substance which resembles the carboxylic acids to a marked degree,[1] simple alkyl halides react with the silver salt much more rapidly by addition than by replacement, it seems probable that the silver carboxylates also react preferentially by addition and that replacement becomes the predominating reaction only when interfering groups retard the rate of addition. The 1,4 addition observed with the quinone derivative is perhaps not an unusual reaction at all; few compounds are conceivable in which the formation of O-ethers by an addition reaction is possible and at the same time capable of detection.

The formation of alkyl hydroxynaphthoquinones bears pronounced resemblance to the C-alkylation of non-tautomeric phenols recently discovered by Claisen.[4] In each case C-alkylation occurs only with the very reactive alkyl halides and the relative yields of O-ethers and C-ethers

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[2] Conant, Kirner and Hussey, THIS JOURNAL, **47,** 488 (1925).

[3] Clarke, *J. Chem. Soc.*, **97,** 416 (1910).

[4] Claisen, *Ann.*, **442,** 210 (1925). Also, *Z. angew. Chem.*, **36,** 478 (1923).

are somewhat the same. Thus Claisen obtained a higher yield of the C-alkyl derivative with cinnamyl and benzyl halides than with allyl bromide, as was also observed in the present case. Diphenyl-bromomethane gave a slightly lower yield of C-alkyl phenol than benzyl chloride; with the quinone salt it gave about the same amount of the C-alkyl derivative as benzyl bromide. Clearly in each case the proportion of the different products obtained from one and same hydroxy compound varies with the nature of the alkyl halide. As Claisen has pointed out, this fact is at variance with those theories of the mechanism of the alkylation of aceto-acetic ester and of similar compounds which assume a tautomerism of the metallic salt in question or of a free radical. The C-alkylation observed in the case of phenol and in the case of the quinone derivative leaves little foundation for the belief that tautomerism is related causally to C-alkylation. The ability of most enolates to form C-alkyl derivatives with saturated alkyl halides is adequately accounted for by the greater reactivity of the double bond in these substances as compared with the double bond of phenolates. With the accumulation of unsaturated groups on the double bond of the enolate its additive power decreases to a point comparable to that of the phenolates.[5]

Indeed, hydroxynaphthoquinone is not to be regarded as a phenol but as a negatively substituted enol, the cyclic structure of which appears to prevent ketonization. It is structurally similar to the enol form of oxalyl-acetic ester, both compounds containing the grouping: —CO—CHOH=CH—CO—. Like this ester it is a strong acid, like the sodium derivative[6] of the ester its sodium salt reacts with alkyl halides only with extreme difficulty, while the silver salts of both substances yield O-ethers exclusively on reaction with saturated alkyl halides.[7] That the hydroxynaphthoquinone silver salt reacts in much the same fashion as sodium phenolate with certain alkyl halides is an indication of the greater additive power of the double linkage in the quinone, for it is well known that addition occurs much less readily with the heavy-metal salts than with sodium salts.

Reactions of Allyl-hydroxynaphthoquinone

The structures of the C-alkyl derivatives obtained may be inferred from the decreased acidity of the hydroxyl group in these compounds. Thus both diphenylmethyl- and triphenylmethyl-hydroxynaphthoquinone are insoluble in aqueous alkalies but dissolve readily in dil. alcoholic alkaline solution. More conclusive evidence is available in the case of the allyl compound, for this was also obtained by the rearrangement of

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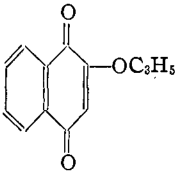
[5] Nef, *Ann.*, **276**, 232 (1893).

[6] Wislicenus and Arnold, *Ann.*, **246**, 336 (1888).

[7] Ref. 5, p. 227.

each of the O-ethers, V and VIII. Like O-allyl-aceto-acetic ester[8] and the negatively substituted phenol allyl ethers,[9] the quinone ethers undergo rearrangement at a relatively low temperature (130–135°). The same product was obtained from each ether and this was identical with the product obtained in the alkylation. Since there is but one position which the allyl group can assume, the substance must have the structure of VII or of the *o*-quinone isomer. The *o*-quinone structure is rejected for reasons given below, and it is not necessary to assume that a substance of this structure is an intermediate product in the conversion of VIII into VII. It seems more probable that a triketone (VI) is the primary product of the rearrangement of each ether[10] and the hydrogen atom of this substance can shift directly to either oxygen according to which position represents the condition of greater stability.



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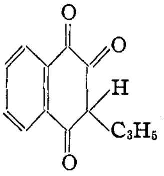
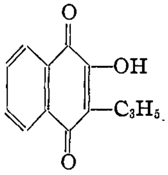
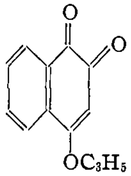


VI

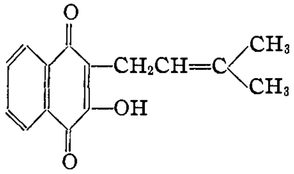


VII



VIII

Allyl-hydroxynaphthoquinone is of particular interest because of its similarity to the natural product lapachol, to which Hooker[11] has assigned the structure of IX. Both substances are yellow, dissolve only to a slight extent in sodium bisulfite solution, and the alkaline solutions of both are red. Employing certain of the methods developed by Hooker[11a] for the preparation of a series of derivatives of lapachol, allyl-hydroxynaphthoquinone was converted into similar compounds under much the same conditions. Thus, the substance was converted by the action of hydrochloric acid in glacial acetic acid solution into a mixture of the hydrochloride (XI) and a non-acidic substance isomeric with X. The substance is yellow and insoluble in bisulfite solution and must, therefore, be a *p*-quinone. The absence of an hydroxyl group, together with the known ease with which *o*-allyl phenols are converted into methylcoumaranes by the action of mineral acids,[12] indicates the structure of the *p*-coumarane-quinone, XII. Similarly, the structure of the hydrochloride, XI, is assumed on the basis of the known rules of addition.



IX

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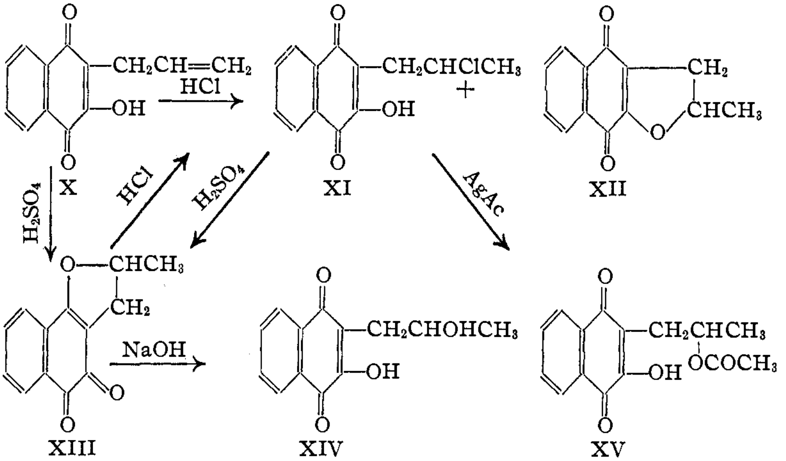
[8] Claisen, *Ber.*, **45**, 3157 (1912).

[9] Claisen and Eisleb, *Ann.*, **401**, 21 (1913). Claisen, *Ann.*, **418**, 69 (1919).

[10] A compound of the type —CO—CHR—CO— is the final product of the rearrangement of O-allyl-aceto-acetic ester.

[11] Hooker, (a) *J. Chem. Soc.*, **61**, 611 (1892); (b) **63**, 1376 (1893); (c) **69**, 1355 (1896).

[12] Claisen, Ger. pat. 279,864.



A second isomer of allyl-hydroxynaphthoquinone is formed by the action of concd. sulfuric acid on this substance. Being red, and readily soluble in bisulfite solution, it is regarded as the *o*-coumarane-quinone derivative, XIII. It dissolves in concd. hydrochloric acid and is converted by this reagent into the hydrochloride, XI. The reverse reaction is brought about by the action of concd. sulfuric acid. The *o*-quinone derivative dissolves readily in dil. sodium hydroxide solution with development of an intensely red color but the process of solution is accompanied by a change in structure, for acids now precipitate a yellow substance which differs in composition from XIII by the elements of water. It is thus regarded as the alcohol, XIV, the acetate of which (XV) may be prepared from XI by means of silver acetate.

It is theoretically possible that all of the above compounds which have free hydroxyl groups are *o*-quinones. However, they are all yellow like the *p*-coumarane-quinone, XII, and they are insoluble or sparingly soluble in bisulfite solution. They are consequently regarded as *p*-quinone derivatives. For similar reasons, the *p*-quinonoid structure has been adopted for all of the C-alkyl-hydroxynaphthoquinones which have been obtained.

Though in the case of lapachol it is presumably the third carbon from the nucleus which enters into combinations corresponding to those above, the only essential difference in the behavior of allyl-hydroxynaphthoquinone and of lapachol is that ring formation and addition to the double bond both take place more readily with this latter compound.

Experimental Part

1. Allyl Derivatives.—Three products are formed in the reaction of the silver salt of hydroxynaphthoquinone with allyl halides and these may be separated by taking advantage of the solubility of the *o*-quinone ether in bisulfite solution and of the acidity of the C-alkyl derivative.

Much time is saved, however, by removing the greater part of the *o*-quinone ether by crystallization.

A suspension of 82 g. of the silver salt in 300 cc. of benzene was boiled with 36 g. of allyl bromide for 20 minutes, when reaction was complete. The solution was filtered, the residue washed out with more benzene, and the combined extract concentrated to a volume of 300 cc. About three-fourths of the *o*-quinone ether separated on cooling. The mother liquor was first extracted with dil. ammonia solution, and then with dil. sodium bisulfite solution. Thus the C-allyl derivative and the remainder of the *o*-quinone ether were removed in succession and were recovered by neutralizing the solutions with acid and with sodium carbonate, respectively. The benzene solution was then dried, concentrated to a volume of 50 cc., and petroleum ether was added. The tarry product which separated was purified by precipitation from benzene solution with petroleum ether, the tar coming down first, and finally crystallized from ligroin. The yields of products melting not more than 3–4° below the correct temperatures were as follows: *o*-quinone ether, 40.1 g.; *p*-quinone ether, 3.7 g.; allyl-hydroxynaphthoquinone, 10.6 g.

When allyl iodide was employed the reaction went to completion with the evolution of heat and without external heating in about five minutes. The average yields obtained in duplicate experiments are indicated in the theoretical part of the paper.

In order to determine whether the C-allyl derivative obtained could have been formed by the rearrangement of the O-ethers, a concentrated benzene solution of the *o*-quinone ether was heated under the reflux condenser and tested from time to time for the presence of the rearrangement product. None of this material could be detected after boiling for three hours, but in five hours a small amount of the substance, together with some decomposition products, had been formed. No rearrangement of the *p*-quinone ether took place on boiling a benzene solution of the substance for one hour. It was concluded that very little rearrangement could occur under the conditions of the experiments recorded, though an experiment with allyl chloride was rejected because the mixture required boiling for about 20 hours to complete the reaction.

4-Alloxy-1,2-naphthoquinone is readily soluble in alcohol, benzene or ether and forms a soluble bisulfite compound. It separates from alcoholic solution in the form of long, orange-yellow needles; m. p., 125°.

Anal. Calcd. for $C_{13}H_{10}O_3$: C, 72.9; H, 4.7. Found: C, 72.6; H, 4.8.

2-Alloxy-1,4-naphthoquinone is somewhat more soluble in the usual solvents than the isomeric ether. It crystallizes from ligroin or from dil. alcohol in the form of pale yellow, flat needles; m. p., 98.5°. This ether was also obtained, although only in about 20% yield, by refluxing for three hours a solution of hydroxynaphthoquinone in allyl alcohol containing 3% of hydrogen chloride.

Anal. Calcd. for $C_{13}H_{10}O_3$: C, 72.9; H, 4.7. Found: C, 72.6; H, 4.8.

2-Allyl-3-hydroxy-1,4-naphthoquinone is best prepared by the rearrangement of the *o*-quinone ether. The reaction commences at a temperature about 5° above the melting point of the substance and is highly exothermic. In consequence, the temperature must be carefully controlled and not more than 5–10 g. of material should be used at a time, otherwise the temperature of the melt rises rapidly to a point where deep-seated decomposition occurs.

A large test-tube containing the ether was heated in an oil-bath maintained at 135°, and the reacting material was protected from the air by a stream of nitrogen. The material, which was constantly stirred with a thermometer, commenced reacting as soon as fusion was complete. The inner temperature was maintained at 140–145° by removing the tube from the bath whenever the temperature started to rise too rapidly. In 30 minutes the inner and outer temperatures were the same and the tube was at once removed, as too long heating causes some decomposition.

The reaction product contains impurities which are not removed by extraction with alkali or by crystallization in the ordinary way. The following method, however, gave excellent results. The product was dissolved in glacial acetic acid and hot water was then added until the solution became slightly turbid. An oil separated, and in a few minutes it had solidified sufficiently to be retained on the filter on filtering the solution by suction. A completely pure product was obtained from the filtrate. Twenty g. of the ether, rearranged in three portions, yielded 14 g. of pure product.

Allyl-hydroxynaphthoquinone is very readily soluble in benzene, alcohol, glacial acetic acid, or ether, and sparingly soluble in petroleum ether. It is somewhat soluble in boiling water, imparting to the solution a pink color which disappears on the addition of a trace of acid. The substance is slightly soluble in bisulfite solution and is precipitated unchanged by acids. It crystallizes best from ligroin or dil. acetic acid, forming beautiful, yellow needles; m. p., 116°. The sodium hydroxide or carbonate solution of the substance is a somewhat deeper shade of red than that of hydroxynaphthoquinone.

Anal. Calcd. for $C_{13}H_{10}O_3$: C, 72.9; H, 4.7. Found: C, 72.8; H, 4.7.

Though the rearrangement of the *p*-quinone ether was studied on a small scale only, it was evident that much less heat was given off than in the case of the isomer. In one experiment the temperature was raised very slowly from 100° to 160° and the inner temperature remained 2–3° below that of the bath throughout, while in another case the rearrangement of 1 g. of material was found to be complete in ten minutes at 135°.

Samples of material obtained by the three methods given were carefully purified and found to be identical.

The following *reactions of allyl-hydroxynaphthoquinone* were studied.

(a) **Acetylation.**—The normal acetyl derivative of this compound has not yet been obtained. The reaction with acetic anhydride and sulfuric acid proceeds in an anomalous fashion giving a red, water-soluble substance, probably a sulfonic acid, which is still under investigation. Acetic anhydride alone is without action, while the reaction with acetic anhydride and sodium acetate appears to proceed abnormally, as the following results show.

On warming a mixture of 3 g. of the quinone, 3 g. of sodium acetate and 20 cc. of acetic anhydride, a red color at first developed which soon changed to brown. After the solution had been boiled for five minutes it was cooled, poured into water, and the crude product crystallized from glacial acetic acid and from alcohol. The material appeared to consist of a mixture of substances, but only one pure product was isolated. This was obtained as the less soluble fraction on fractional crystallization from benzene. The compound dissolves readily in benzene and is sparingly soluble in alcohol or ligroin. It crystallizes from benzene in the form of rosets of thick needles, while long, hair-like, colorless needles are deposited from the alcoholic solution; m. p., 220–221°, with decomposition. The substance is hydrolyzed with boiling sodium hydroxide solution and in the presence of the air the solution becomes red and a red substance is precipitated on neutralization.

Anal. Calcd. for (a) $C_{15}H_{12}O_4$: C, 70.3; H, 4.7; (b) $C_{17}H_{14}O_5$: C, 68.4; H, 4.7. Found: C, 68.2, 68.0; H, 4.8, 4.7.

While the values do not agree at all with those calculated for the mono-acetate (a) they are in fairly good agreement with the formula $C_{17}H_{14}O_5$. This differs from the formula of the quinone by the increment $C_4H_4O_2$; thus two acetyl groups have been introduced and two hydrogen atoms eliminated.

The substance is thus analogous to that obtained from lapachol in the same manner by Paternò and Minunni,[13] for this compound as Hooker has shown[14] differs in composition from lapachol by the same increment and possesses the properties of a hydroquinone diacetate. Inasmuch as Dr. Hooker has informed me that the structure of the lapachol derivative is under further investigation in his Laboratory, I have not studied further the substance described above.

The **hydroquinone triacetate** was prepared by reduction of allyl-hydroxynaphthoquinone with zinc and acetic acid in the presence of acetic anhydride. It is readily soluble in alcohol or benzene and is best crystallized from a benzene-ligroin mixture. Small, colorless prisms, m. p. 155.5°, were obtained.

Anal. Calcd. for $C_{19}H_{18}O_6$: C, 66.7; H, 5.3. Found: C, 66.8; H, 5.4.

(b) Reaction with Hydrogen Chloride.—On subjecting allyl-hydroxynaphthoquinone to the treatment which Hooker[11a] found most satisfactory for the preparation of the hydrochloride of lapachol, the material was recovered unchanged. The hydrochloride together with a small amount of the methylcoumarane derivative was obtained by more prolonged heating, as follows.

Twenty-five cc. of concd. hydrochloric acid was added to a solution of 5 g. of the quinone in 50 cc. of glacial acetic acid and the mixture warmed on the water-bath. The material which at first precipitated soon dissolved, giving a brown-red solution. After heating for three hours the solution was cooled and 100 cc. of concd. hydrochloric acid was added. The precipitate, which proved to be the hydrochloride, was collected and washed with hydrochloric acid and then with water; yield, 4.50 g.; m. p., 146–147°. The addition of water to the filtrate caused the separation of a reddish product which was found to be the *p*-coumarane-quinone in somewhat impure condition; yield, 0.45 g.; m. p., 157°.

The hydrochloride, **2-(β-chloro-propyl)-3-hydroxy-1,4-naphthoquinone** (XI), crystallized from benzene-ligroin in the form of thick, canary-yellow needles; m. p., 147°.

Anal. Calcd. for $C_{13}H_{11}O_3Cl$: Cl, 14.2. Found: 14.0.

The substance dissolves readily in dil. alkalies with development of a deep red color. It may be obtained from the *o*-coumarane-quinone and hydrochloric acid, as shown below. The ACETYL DERIVATIVE was prepared by short heating with acetic anhydride containing a trace of sulfuric acid. It is moderately soluble in ligroin, from which solvent it separates in the form of pale yellow needles; m. p., 102°.

Anal. Calcd. for $C_{15}H_{13}O_4Cl$: Cl, 12.1. Found: 12.1.

1-Methyl-4,5-benzo-3,6-coumarane-quinone (XII).—The crude product obtained

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[13] Paternò and Minunni, *Gazz. chim. ital.*, **19**, 607 (1889).

[14] Ref. 11 a, p. 624.

in the manner described above was crystallized repeatedly from benzene, but the last traces of dark colored impurities were only removed by crystallization from ligroin with the liberal use of animal charcoal. The substance was then obtained in the form of slender, pale yellow needles; m. p., 166–167°.

Anal. Calcd. for $C_{13}H_{10}O_3$: C, 72.9; H, 4.7. Found: C, 72.7; H, 4.8.

The compound dissolves readily in benzene and to a less extent in ligroin. It is insoluble in dil. sodium hydroxide solution in the cold, but dissolves slowly on boiling to a deep red solution. The solution in concd. sulfuric acid is of a much deeper shade of red than that of the isomeric *o*-quinone, and the substance may be recovered unchanged after the solution has stood for several hours in the cold, or after gentle warming. Dil. bisulfite solution does not dissolve the material.

This compound was also obtained, though in very small amounts, by boiling a solution of the above-mentioned hydrochloride in glacial acetic acid for four hours, and the material was identified by a mixed-melting-point determination.

(c) Ring Closure with Sulfuric Acid.

1-Methyl-3,4-benzo-5,6-coumarane-quinone (XIII).—Allyl-hydroxynaphthoquinone was dissolved in 5 parts of concd. sulfuric acid, which was cooled to room temperature, and after five minutes the deep red solution was poured into water. After the acid had been partially neutralized with aqueous ammonia, the bright red precipitate which had formed was collected, dissolved in sodium bisulfite solution and precipitated with sodium carbonate. This process of purification is accompanied by the loss of some material due, probably, to the action of the excess of sodium carbonate. The substance is readily soluble in the usual solvents except ligroin, and it dissolves to a slight extent in water. The solution in benzene-ligroin deposits small red needles; m. p., 133.5°.

Anal. Calcd. for $C_{13}H_{10}O_3$: C, 72.9; H, 4.7. Found: C, 72.6; H, 4.8.

This compound was also obtained in good yield by heating a solution of 1 g. of chloropropyl-hydroxynaphthoquinone in 5 cc. of concd. sulfuric acid at 80° for one-half hour. The crude material, obtained by pouring the solution into water, melted at 131–132°. The reverse reaction was brought about in the following manner.[15]

One g. of the *o*-coumarane-quinone was dissolved in 30 cc. of concd. hydrochloric acid and the solution maintained at a temperature of 55° for one hour. The initially red solution slowly became yellow and small crystals were deposited. After being warmed to 65° for one-half hour, the mixture was cooled. The precipitate, which was washed with concd. hydrochloric acid and with water, was nearly pure chloropropyl-hydroxynaphthoquinone (m. p., 146°) and the conversion was quantitative.

The *o*-coumarane-quinone derivative is more easily attacked by alkalies than is β-lapachone, being completely dissolved in the cold. Neutralization of the deep red solution caused the separation of an oil which, in the course of a few hours, changed into a mass of light yellow crystals. The substance dissolves very readily in benzene or alcohol and is best crystallized from dil. methyl alcohol, from which solvent there are deposited fine, pale yellow needles. The melting point is 108–110°. The properties and analysis of the compound indicate that it is **2-(β-hydroxypropyl)-3-hydroxy-1,4-naphthoquinone** (XIV).

Anal. Calcd. for $C_{13}H_{12}O_4$: C, 67.2; H, 5.2. Found: C, 67.5; H, 5.5.

An acetyl derivative (XV) was prepared by heating a solution of chloropropyl-hydroxynaphthoquinone in glacial acetic acid with one equivalent of silver acetate. After the mixture had been filtered from the silver chloride, an oil which slowly solidified

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[15] Under these conditions β-lapachone is transformed into α-lapachone. See Ref. 11 a.

was precipitated by the addition of water. The substance is very readily soluble in the usual solvents and does not crystallize well. It was obtained as a fine crystalline powder by the use of ether and petroleum ether; m. p., 127°.

Anal. Calcd. for $C_{15}H_{14}O_5$: C, 65.7; H, 5.1. Found: C, 65.6; H, 5.3.

2. Benzyl Derivatives.—The reaction of benzyl bromide with the silver salt of hydroxynaphthoquinone (10 g.) was carried out in benzene suspension as before, but the isomeric ethers could not be separated by means of bisulfite solution because the *o*-quinone benzyl ether is only sparingly soluble in a solution of this reagent. The most successful procedure was as follows.

On concentrating the benzene solution of the reaction product to a volume of 100 cc. most of the *o*-quinone ether and some of the C-benzyl derivative deposited on cooling. The two were easily separated by solution of the latter substance in ammonium hydroxide solution and the remainder of the benzyl-hydroxynaphthoquinone was extracted from the benzene mother liquor with ammonia solution. The benzene solution was then dried, concentrated to a small volume, and petroleum ether added. The material which separated, after preliminary purification, was separated by fractional crystallization from ligroin into the pure *o*-quinone ether (1 g.) and a second substance (1 g.) which, by the constancy of its melting point and the homogeneity of the crystals, appeared to be a pure compound. However, on crystallization from 85% alcohol containing a little hydrochloric acid, a small amount of hydroxynaphthoquinone was formed and the melting point was 3° higher. Since no further hydrolysis took place on a further crystallization, and since the isomeric ether is completely hydrolyzed under these conditions, the final product is regarded as the pure *p*-quinone ether; yields: *o*-quinone ether, 4.8 g.; *p*-quinone ether, 0.8 g.; C-benzyl derivative, 2.2 g.

4-Phenylmethoxy-1,2-naphthoquinone crystallized from benzene in the form of thick, orange-yellow needles; m. p., 182.5°. It is moderately soluble in benzene, sparingly soluble in ligroin or alcohol, sparingly soluble in bisulfite solution and readily hydrolyzed by acids.

Anal. Calcd. for $C_{17}H_{12}O_3$: C, 77.2; H, 4.6. Found: C, 77.1, H, 4.7.

2-Phenylmethoxy-1,4-naphthoquinone forms long, pale yellow needles; m. p., 145°. It is slighly more soluble in organic solvents than the isomeric ether.

Anal. Calcd. for $C_{17}H_{12}O_3$: C, 77.2; H, 4.6. Found: C, 77.0; H, 4.8.

2-Benzyl-3-hydroxy-1,4-naphthoquinone.—The material obtained as described above (m. p., 170–171°) was crystallized from benzene-ligroin; it formed beautiful, golden-yellow plates melting at 175–176°. It separates from alcoholic solution containing a little acid in the form of needles. The compound dissolves readily in benzene, alcohol or glacial acetic acid, and it dissolves in sodium hydroxide or carbonate solution (with some difficulty) with a red color similar in shade to that of solutions of allylhydroxynaphthoquinone.

Anal. Calcd. for $C_{17}H_{12}O_3$: C, 77.2; H, 4.6. Found: C, 76.9; H, 4.7.

3. Diphenylmethyl Derivatives.—On adding 9.5 g. of diphenylbromomethane[16] to a suspension of 10 g. of the silver salt and 2 g. of sodium carbonate in 75 cc. of benzene, a rapid reaction took place and the solution warmed considerably. The mixture was shaken for two hours to insure complete conversion of a few red particles which remained unattacked. As preliminary experiments had shown that hydroxynaph-

[16] Prepared from the hydrocarbon according to Nef, *Ann.*, **298**, 232 (1897).

thoquinone, the C-alkyl derivative and the *p*-quinone ether were formed in this reaction, the following method of working up the mixture was adopted. The benzene solution, after removal of the silver bromide, was extracted thoroughly with ammonia solution to remove the two acidic substances. The mixture obtained on neutralizing the extract was dried, finely powdered and shaken with very dilute ammonia solution. Since diphenylmethyl-hydroxynaphthoquinone is much less readily soluble than the parent compound in ammonia solution, all of the latter substance went into solution on the first treatment and was recovered in fairly pure condition (m. p., 183°, decomp.) while only a small amount of the C-alkyl derivative was dissolved by a fresh portion of ammonia solution. The benzene mother liquor now contained, besides a little tar, only the *p*-quinone ether, and this was readily isolated by concentrating the solution and adding ligroin; yields: hydroxynaphthoquinone, 0.6 g.; *p*-quinone ether, 6.3 g.; C-alkyl derivative, 2.5 g. In calculating the percentage yields given above, the amount of the silver salt equivalent to the hydroxynaphthoquinone formed was deducted from the amount taken.

2-Diphenylmethoxy-1,4-naphthoquinone.—The crude product was crystallized from alcohol, in which it is sparingly soluble; better from benzene, which readily dissolves the material. A thick crust of pale yellow crystals was deposited from the latter solvent; m. p., 150–151°. Hydrolysis of the ether is readily accomplished by boiling alkali but not by 85% alcohol, 0.1 *N* in hydrogen chloride. It follows from these properties that the compound is the *p*-quinone ether.

Anal. Calcd. for $C_{23}H_{16}O_3$: C, 81.1; H, 4.7. Found: C, 80.9; H, 4.8.

2-Diphenylmethyl-3-hydroxy-1,4-naphthoquinone.—The crude product (m. p., 184–185°) was crystallized repeatedly from benzene-ligroin, when it melted at 186.5°. The substance is very readily soluble in benzene or glacial acetic acid, moderately soluble in alcohol, ligroin or ether. It does not crystallize well but forms a powder of yellow micro-needles. While practically insoluble in aqueous alkali solution, it readily dissolves in 50% alcohol containing 1% of sodium hydroxide.

Anal. Calcd. for $C_{23}H_{16}O_3$: C, 81.1; H, 4.7. Found: C, 81.0; H, 4.8.

This compound may be prepared more easily by a curious reaction discovered by Möhlau and Klopfer[17] and applied by them to certain unsubstituted *p*-quinones. A solution of 20 g. of hydroxynaphthoquinone and 20 g. of benzohydrol in 150 cc. of glacial acetic acid containing 2 cc. of concd. sulfuric acid was boiled for two hours, a little water was then added and the solution was allowed to cool. Thirty-eight g. of material, m. p. 185°, separated. The product was identical with that obtained above.

The ACETYL DERIVATIVE was obtained by the action of acetic anhydride containing a little sulfuric acid on the hydroxy compound. It dissolved readily in benzene and crystallized from this solvent, best after adding ligroin, in the form of large, yellow rosets; m. p., 170.5°.

Anal. Calcd. for $C_{25}H_{18}O_4$: C, 78.5; H, 4.7. Found: C, 78.3; H, 4.7.

The HYDROQUINONE TRIACETATE, prepared by boiling a mixture of the quinone, zinc dust, acetic anhydride and acetic acid for one-half hour, crystallized from benzene in the form of aggregates of colorless needles; m. p., 215°.

Anal. Calcd. for $C_{29}H_{24}O_6$: C, 74.3; H, 5.2. Found: C, 74.3; H, 5.3.

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[17] Möhlau and Klopfer, *Ber.*, **32,** 2146 (1899).

4. **2-Triphenylmethyl-3-hydroxy-1,4-naphthoquinone.** The silver salt of hydroxynaphthoquinone, suspended in benzene, reacted almost completely with triphenyl-chloromethane at room temperature in about five minutes. Only one substance, the C-alkyl derivative, appeared to be formed and this was separated from a small amount of tar by crystallization; yield from 10 g. of the silver salt, 12.5 g. (pure).

The substance is readily soluble in benzene, sparingly soluble in ligroin or alcohol. It crystallizes best from benzene-ligroin, forming a crust of yellow needles melting at 211° with decomposition.

Anal. Calcd. for $C_{29}H_{20}O_3$: C, 83.6; H, 4.8. Found: C, 83.5; H, 4.9.

The compound is not soluble in aqueous alkali but dissolves readily with a red color in 50% alcohol containing 1% of sodium hydroxide. Acids precipitate the original material, while the addition of an excess of alkali to the solution causes the separation of the sodium salt. This was crystallized from dil. alcohol and was so obtained in the form of small, dark red prisms.

Anal. Calcd. for $C_{29}H_{19}O_3Na$: Na, 5.2. Found: 4.8.

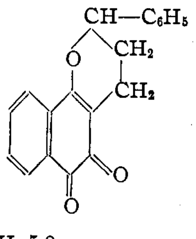
5. **2-Cinnamyl-3-hydroxy-1,4-naphthoquinone.**—After several attempts to find a satisfactory procedure for the cinnamylation of hydroxynaphthoquinone and for the isolation of the product, the following methods was adopted, though the results still leave much to be desired.

A mixture of 10 g. of the silver salt, 6 g. of cinnamyl chloride,[18] m. p. 8°, 2 g. of sodium carbonate, and 75 cc. of benzene was shaken mechanically for four hours. After removal of the inorganic material, the benzene solution was concentrated and cooled. The material separating was the nearly pure C-alkyl derivative. Evaporation of the mother liquor left a dark oil which largely dissolved in 50% alcohol containing 1% of sodium hydroxide. On acidifying the solution so obtained, the material separated in the form of an oil, but crystallization from glacial acetic acid gave a further quantity of the C-alkyl derivative. No other substance could be isolated from the residual tar in this experiment or in others. The combined product obtained was crystallized from dil. acetic acid in the manner used in purifying the allyl derivative; yield, 5.3 g.

Cinnamyl-hydroxynaphthoquinone is readily soluble in glacial acetic acid, moderately soluble in alcohol or benzene, insoluble in water. It dissolves with difficulty in sodium hydroxide solution with development of a red color, and acids precipitate the material in the form of a fine powder which coagulates on standing. It separates from dil. acetic acid solution or from alcohol in the form of lustrous, yellow needles; m. p., 170°. On exposure to the action of sunlight the substance rapidly turns brown.

Anal. Calcd. for $C_{19}H_{14}O_3$: C, 78.6; H, 4.9. Found: C, 78.7; H, 5.0.

A derivative of this compound, probably **2-phenyl-7,8-benzo-5,6-chromane-quinone**, was obtained in the following manner. One g. of cinnamyl-hydroxynaphthoquinone was dissolved in 5 cc. of concd. sulfuric acid and after ten minutes the dark red solution was poured into water. The orange-red product which precipitated was crystallized from alcohol, benzene and benzene-ligroin and was thus obtained in the form of clusters of bright red needles; m. p., 167°. It is very readily soluble in benzene, readily soluble in alcohol, sparingly soluble in ligroin.



Anal. Calcd. for $C_{19}H_{14}O_3$: C, 78.6; H, 4.9. Found: C, 78.8; H, 5.0.

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[18] Rupe and Bürgin, *Ber.*, **43,** 173 (1910).

The substance, which is isomeric with cinnamyl-hydroxynaphthoquinone, is insoluble in cold sodium hydroxide solution and is dissolved with change on boiling. The red color indicates an *o*-quinonoid structure, though the compound does not dissolve to an appreciable extent in bisulfite solution. The above structure is provisionally assigned to the compound on the basis of the analogy between cinnamyl-hydroxynaphthoquinone and lapachol.

Summary

1. 2-Alkyl-3-hydroxy-1,4-naphthoquinones are formed, in yields varying with the nature of the alkyl halide employed, in the reaction of the silver salt of hydroxynaphthoquinone with allyl, cinnamyl, benzyl, diphenylmethyl, and triphenylmethyl halides. In some cases isomeric *p*-quinone and *o*-quinone O-ethers are also formed. In general, the amount of the C-alkylation product increases with increasing reactivity of the alkyl halide.
2. Allyl-hydroxynaphthoquinone is very similar in properties and reactions to lapachol.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF YALE UNIVERSITY]

SOME AMIDINES OF THE HOLOCAINE TYPE

II. ESTER-SUBSTITUTED AMIDINES[1]

BY ARTHUR J. HILL AND MILDRED V. COX[2]

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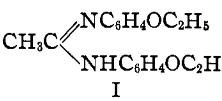
The first paper[3] of this series dealt with the synthesis of homologs of the local anesthetic "Holocaine I," in which the methyl group of this compound was replaced by other alkyl radicals. The object of the present investigation has been to replace certain portions of the holocaine molecule with amino ester groups,[4] taking cognizance of the fact that most important local anesthetics are amino esters. Theoretically, this type of replacement should decrease the characteristic toxicity and irritability of holocaine and yet maintain its anesthetic efficiency.



$$CH_3C\begin{cases} NC_6H_4OC_2H_5 \\ NHC_6H_4OC_2H_5 \end{cases}$$

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To this end, two types of ester-substituted amidines have been prepared, the type formulas of which are given below.

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[1] This investigation has been conducted in coöperation with the National Research Council Sub-Committee on Local Anesthetics. It was presented in part before the Medicinal Product Section of the American Chemical Society at the Washington meeting, April, 1924.

[2] This paper is constructed from the dissertation presented by Mildred V. Cox to the Faculty of the Graduate School of Yale University in partial fulfilment of the requirements for the degree of Doctor of Philosophy, 1925.

[3] Hill and Rabinowitz, THIS JOURNAL, **48,** 732 (1926).

[4] Ester-substituted derivatives of diphenyl formamidine, possessing local anesthetic properties, have been described by Goldschmidt [*Chem.-Ztg.*, **26,** 743 (1902)].