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).

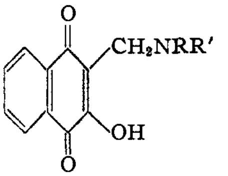
CAMBRIDGE 38, MASSACHUSETTS RECEIVED MAY 13, 1947

[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-

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(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).

TABLE I

2-HYDROXY-3-SUBSTITUTED-AMINOMETHYL-1,4-NAPHTHOQUINONES

Code no.	3-Substituent	M. p., °C.[a]	Yield, %	Formula	Nitrogen, %	
					Calcd.	Found
M-353	$-CH_2NHC_4H_9$-*n*	158–159[b]	75	$C_{15}H_{17}NO_3$	5.40	5.31
M-346	$-CH_2NHC_5H_{11}$-*n*	159–160[b]	66	$C_{16}H_{19}NO_3$	5.13	5.26
					C, 70.33	70.75
					H, 6.96	6.98
M-354	$-CH_2NHC_{10}H_{21}$-*n*	148–149[b]	96	$C_{21}H_{29}NO_3$	4.08	3.98
M-363	$-CH_2NHCH_2C_6H_5$	149–150[b]	83	$C_{18}H_{15}NO_3$	4.78	4.85
M-347	$-CH_2NH$-cyclohexyl	185–190[c]	98	$C_{17}H_{19}NO_3$	4.91	4.56
M-360	$-CH_2NHCH_2CH_2OH$	168–169[b]	71	$C_{13}H_{13}NO_4$	5.67	5.67
M-336	$-CH_2N(CH_3)_2$	194–195[b]	87	$C_{13}H_{13}NO_3$	6.06	5.89
M-344	-Piperidinomethyl	196–197[d]	96	$C_{16}H_{17}NO_3$	5.16	5.20
M-361	-2-Me-piperidinomethyl	165–166[b]	74	$C_{17}H_{19}NO_3$	4.91	4.81
M-362	-4-Me-piperidinomethyl	183.5–184[b]	95	$C_{17}H_{19}NO_3$	4.91	4.92
M-345	-Morpholinomethyl	185–186[e]	96	$C_{15}H_{15}NO_4$	5.13	5.16
M-355	$-CH_2NH$-5-(5-Me-dioxanyl)	195–196[b]	97	$C_{16}H_{17}NO_5$	4.62	4.62

[a] Melting points are uncorrected. [b] Recrystallized from dilute alcohol. [c] Recrystallized from dilute isopropanol. [d] Recrystallized from dilute methanol. [e] Because of its instability, this morpholino-analog was purified by solution in cold 2% hydrochloric acid, followed by precipitation of the product from the cold filtered solution with sodium acetate solution.

larly in the case of the morpholine derivative (M-345, Table I) it was desirable to effect purification by first dissolving the crude material in cold 2% hydrochloric acid followed by precipitation with cold sodium acetate solution.

As pointed out above, not all of the amines tried underwent the Mannich reaction with lawsone. And it has been noted before[2] that there are a number of unexplained cases where the Mannich reaction does not take place with relatively simple amines. In this study diethylamine failed to react; on the other hand, dimethylamine and piperidine gave 87 and 96% yields, respectively. In the attempt to condense diethylamine with lawsone and formaldehyde, the product formed was simply the diethylamine salt of 2-hydroxy-3,3'-methylenebis-1,4-naphthoquinone. Dibutylamine and hexamethylene imine behaved similarly but thialdine[4] gave only a tarry product.

Antimalarial Activity.[5]—A more detailed report on the activity of the quinones listed in Table I will be found in Paper II of this series. In general it may be stated, however, that none of these "Mannich bases" approached quinine in activity against *P. lophurae* in ducks. The most active member in the series was M-344, 2-hydroxy-3-piperidinomethyl-1,4-naphthoquinone, Q = 0.37. The dimethylaminomethyl analog, M-336, was still less active and a number of the other members of the series were completely inactive.

Experimental

Preparation of 2-Hydroxy-3-substituted-aminomethyl-1,4-naphthoquinones.—The preparation of the basically substituted naphthoquinones listed in Table I was carried out according to the following general procedure:

In a 250-cc. three-necked flask, fitted with a mechanical stirrer, thermometer and reflux condenser, was placed 0.11 mole of the desired amine in 150 cc. of absolute ethanol.[6] To the stirred solution, 17.4 g. (0.1 mole) of 2-hydroxy-1,4-naphthoquinone (lawsone) was added. The resulting solution was cooled and maintained at 15–20° during the dropwise addition of 8.5 cc. of 37% formalin.

After the formalin had been added, the reaction mixture was allowed to stir at room temperature for one hour was warmed on the steam-bath for an additional hour, and was then left at room temperature overnight. The heavy, deep-red precipitate which formed was separated by filtration, washed with a small amount of cold water and air-dried. If the condensation had proceeded normally, a test sample dissolved completely in dilute hydrochloric acid. The crude product thus obtained was purified by recrystallization from the appropriate solvent given in Table I.

Attempted Mannich Reaction with Diethylamine on Lawsone.—Using 8.0 g. (0.11 mole) of diethylamine, the Mannich reaction with lawsone was carried out according to the general procedure described directly above. However, the red solid which separated at the end of the reaction amounted to only 5.9 g. and a test portion gave a strong odor of amine on treatment with cold sodium hydroxide solution. Treatment with cold dilute hydrochloric acid converted the red solid to a yellow, acid-insoluble compound. The latter after recrystallization from valerolactone melted with decomposition at 249–251° and when mixed with an authentic sample[7] of 2-hydroxy-3,3'-methylene-bis-1,4-naphthoquinone (m. p. 249–251° dec.) there was no depression in the melting point.

Acknowledgment.—The authors wish to thank Mr. E. F. Shelberg and Mr. L. F. Reed of the Microanalytical Department for the microanalyses.

Summary

The Mannich reaction with 2-hydroxy-1,4-naphthoquinone is described for the preparation of 2-hydroxy-3-substituted-aminomethyl-1,4-naphthoquinones.

NORTH CHICAGO, ILL. RECEIVED MAY 13, 1947

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(4) Supplied by the Carbide and Carbon Chemicals Corporation.

(5) All antimalarial evaluations were carried out under the supervision of Richardson and Hewitt, University of Tennessee, O. S. R. D. Contract OEMcmr 481.

(6) Absolute alcohol was used to decrease the solubility of the product as much as possible.

(7) Supplied by Dr. L. F. Fieser.