[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Naphthoquinone Antimalarials. Mannich Bases Derived from Lawsone

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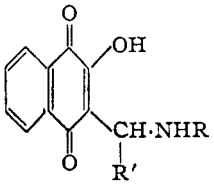
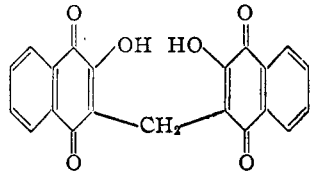
The participation of lawsone (2-hydroxy-1,4-naphthoquinone) in the Mannich reaction to give bases of type (I, R′ = H) has already been reported by Leffler and Hathaway.[2] These authors found that the reaction proceeded readily using formaldehyde with, as the basic component, either primary aliphatic amines of relatively low molecular weight, or certain secondary amines such as dimethylamine, piperidine, morpholine, and various derivatives of the latter two. On the other hand, diethylamine, dibutylamine, and hexamethyleneimine gave only the amine salts of methylene-bis-lawsone (3,3′-methylene-bis-2-hydroxy-1,4-naphthoquinone, II).



(I)



(II)

The Mannich bases obtained by Leffler and Hathaway were found to have little or no antimalarial activity. Earlier papers in this series[3] have, however, shown that the deactivating effect, relative to antimalarial activity, of a hetero-atom in a side chain attached to the 3 position of the lawsone molecule may be overcome by increasing the size of the side chain. The purpose of the present investigation was therefore to make derivatives of lawsone having a large nitrogen-containing substituent in the 3 position.

To this end there were prepared a number of Mannich bases derived from higher primary aliphatic amines. Products were obtained in excellent yields when the reaction was allowed to proceed at room temperature, but the use of the conditions described by Leffler and Hathaway[2] resulted in considerable formation of tar. Moreover the higher members underwent decomposition to brown impurities on attempted recrystallisation from solvents such as ethanol. On treatment with dilute hydrochloric acid yellow hydrochlorides were formed, insoluble in water but soluble in hot ethanol and thereby distinguishable from the almost insoluble methylene-bis-lawsone. The products were conveniently purified by ethanol recrystallisation of their hydrochlorides, which proceeds without decomposition, followed by regeneration of the free base. Leffler and Hathaway considered the dissolution of a product in dilute hydrochloric acid as diagnostic for the formation of a Mannich base, as distinct from the very similar appearing salts of methylene-bis-lawsone. The insolubility of the higher Mannich bases in dilute hydrochloric acid therefore led to some initial confusion, the more so as on attempted recrystallisation of the bases from acetic acid there was rapidly deposited an almost theoretical yield of (II). This was later found to be a general property of all the Mannich bases derived from formaldehyde (including those prepared by Leffler and Hathaway) and is considered to be due to reversal of the Mannich reaction followed by recombination of the lawsone and the aldehyde under the acid conditions. The matter is further considered below.

Attempts to prepare Mannich bases from higher secondary aliphatic amines gave rise solely to the bis-amine salts of (II), these products in some cases undergoing dissociation to the mono-amine salts on recrystallisation. Though secondary amines may give either compounds of type (I) or salts of (II), the products, formed in high yield, always proved homogeneous. Thus while diethylamine gave solely a salt of (II), dimethylamine gave a Mannich base.[2] Attempts were made, using *n*-dodecylamine, to alter the course of the reaction by altering the conditions. No trace of a product other than the Mannich base could be detected when the order of mixing of the reactants was varied, or when the reaction temperature was varied between 5 and 50°, though the method described in the experimental section was found to be best. When dodecylamine hydrochloride was used the amine took no part in the reaction, the lawsone and formaldehyde reacting together to give a high yield of (II). Unlike most Mannich reactions formaldehyde could not be replaced by paraformaldehyde, which gave no product when used alone, and gave (II) if acid was present. The use of aromatic amines in the reaction readily gave high yields of amorphous products which were deeply colored, extremely insoluble, and decomposed on attempted purification. Their extreme insolubility rendered them useless for biological testing and they were not further investigated. Compounds of this type were given by aniline, *p*-aminodiphenyl and phenyl-β-naphthylamine. It is interesting to note that the product from the latter secondary amine was not a salt of (II). However the Mannich reaction of a phenol and an aromatic amine may not necessarily give a Mannich base, but rather a rearrangement product of it.[4] When *p*-nitraniline was used the product could be separated into high yields of

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(2) Leffler and Hathaway, THIS JOURNAL, 70, 3222 (1948).

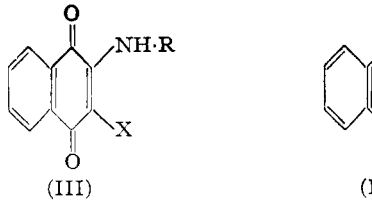
(3) See Fieser, Leffler and co-workers, *ibid.*, 70, 3151 (1948).

(4) Corley and Blout, *ibid.*, 69, 755, 761, 763 (1947).

(II) and methylene-bis-*p*-nitraniline, presumably because the *p*-nitraniline was too weakly basic to form a salt with lawsone initially. A good product of reasonable solubility was given by 2-aminopyridine, but the corresponding product from 6-methoxy-8-aminoquinoline was again too insoluble for biological testing. Very insoluble dark-colored products, unsuitable for testing and not further investigated, were also given by polyamines such as diethylenetriamine and triethylenetetramine.

The investigation was then extended in order to get some idea of the permissible variations in the carbonyl component in the reaction. Replacement of formaldehyde by benzaldehyde gave excellent products of type (I, R′ = C_6H_5) when primary aliphatic amines or 2-aminopyridine were used. However, piperidine, which gives a Mannich base when formaldehyde is used,[2] gave a product analysing for the bis-piperidinium salt of benzylidene-bis-lawsone. Formaldehyde could similarly be replaced by acetaldehyde to give products of type (I, R′ = CH_3) with primary aliphatic amines and 2-aminopyridine. However, with propionaldehyde or crotonaldehyde and either primary or secondary aliphatic amines only tars were produced. The amines could be isolated from these tars as their hydrochlorides and therefore presumably did not take part in the reaction except in salt formation, the tars being of the same type as those known to be formed from lawsone and aliphatic aldehydes under certain conditions.[5] The use of acetophenone as the carbonyl component gave no product, and glyoxal gave only a minute yield. No Mannich reaction occurred when lawsone was replaced by phthiocol.

Various attempts were made to prepare compounds of type (III, X = OH). Naphthoquinone is well known to react with amines to give alkylaminonaphthoquinones (IV). By similar reaction of amines with lawsone it was therefore hoped to obtain the required products. On cooling the red ethanolic solution of an amine and lawsone the red-brown amine salt was obtained, but if the solution was refluxed for some time a dark brown color was found to develop, and a dark brown product separated on cooling. This proved to be the alkylaminonaphthoquinone (IV) identical with the product obtained from the same amine and naphthoquinone itself. By the reaction of amines with 2,3-dichloronaphthoquinone compounds of type (III, X = Cl) were readily obtained, but on hydrolysis these gave chlorolawsone and the amine, none of the required product being formed. In general compounds of types (III) and (IV) behaved as amides rather than amines. Thus they were readily hydrolyzed and did not give hydrochlorides. Attempts to form the naphthoquinone oxide from compounds of type (IV), which might be expected to rearrange to (III), were unsuccessful, and as the results then becoming available showed the lack of antimalarial activity on the part of naphthoquinones with nitrogen-containing substituents the topic was not further pursued.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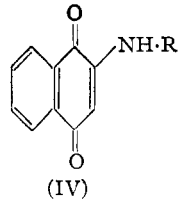
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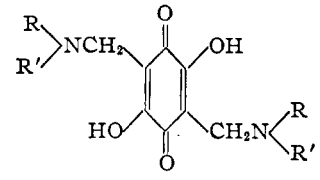
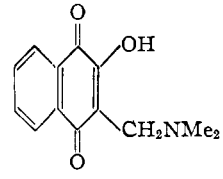
The Mannich reaction was also found to proceed satisfactorily with 2,5-dihydroxy-1,4-benzoquinone, giving derivatives of type (V). With increasing size of the substituent groups in the 3,6 positions the molecule rapidly became extremely insoluble, and useless for biological testing.


(V)

The compound (VI), 2-hydroxy-3-dimethylaminomethyl-1,4-naphthoquinone, is a substituted allylamine and also related to benzylamine. Either (VI) or its quaternary salts might therefore be expected to act as alkylating agents, just as leucotrope (VII, R = $C_6H_5CH_2$) or the corresponding allyl derivative (VII, R = $CH_2{=}CHCH_2$) will alkylate sulfur-containing groups such as thiocyanate,[6] and gramine (VIII) will alkylate acetamidomalonic ester under alkaline conditions.[7] Attempts to carry out any reactions of the above type (see Experimental for details) always led to the production of (II), again presumably due to reversal of the Mannich reaction. Mannich bases are known to decompose readily to the corresponding unsaturated derivative,[8] in some cases this decomposition occurring spontaneously. Compounds of the type $RCOCH_2CH_2NR_2'$ decompose readily with loss of amine in dilute alkaline solution,[8] and similar decomposition is probably responsible for the lack of antimalarial activity of compounds in the present series.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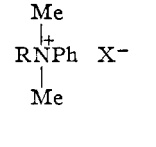
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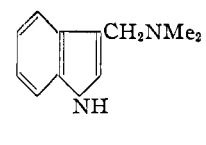

(VIII)

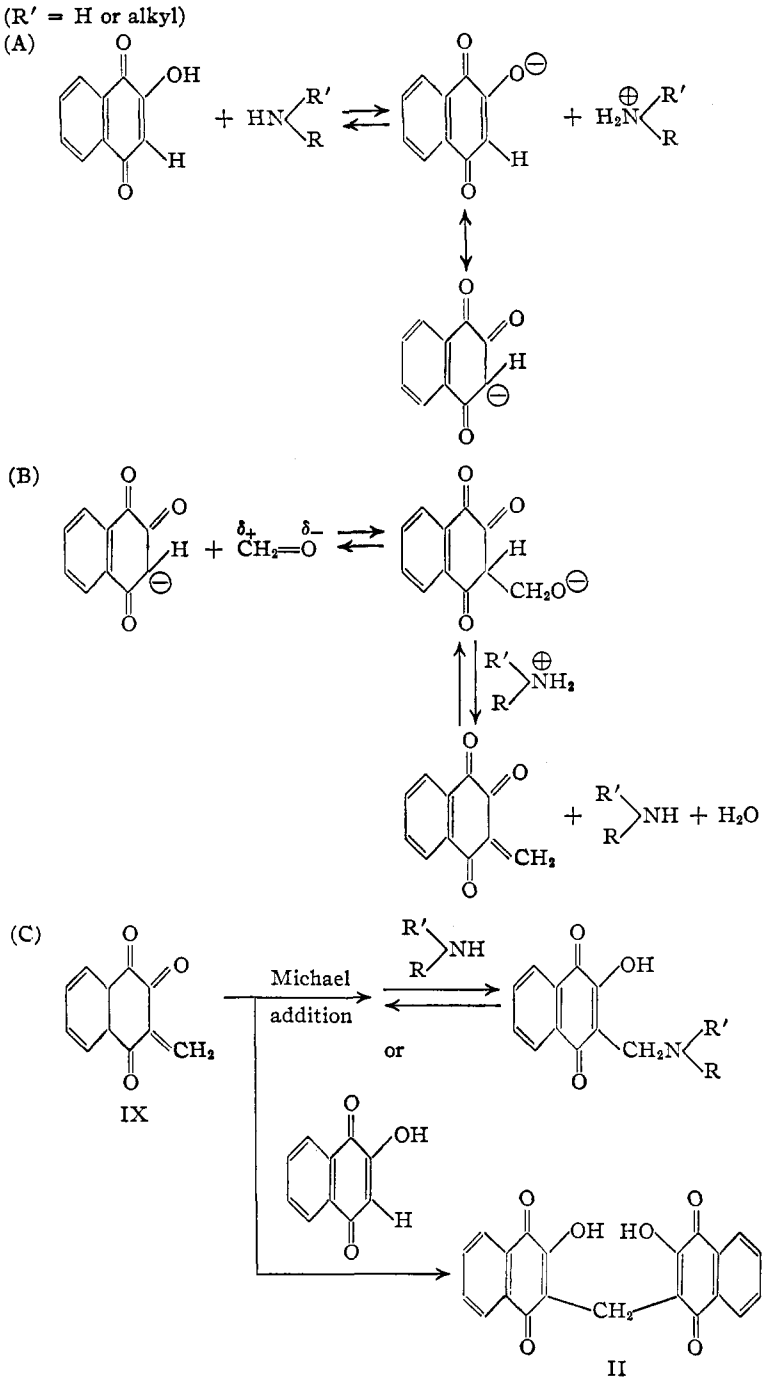
The mechanism of the Mannich reaction is still obscure, it being uncertain whether the

(5) Hooker, THIS JOURNAL, **58**, 1163 (1936).

(6) Snyder and Speck, *ibid.*, **61**, 668, 2895 (1939).

(7) Howe, Zambito, Snyder and Tishler, *ibid.*, **67**, 38 (1945).

(8) Blicke, in "Organic Reactions," **1**, 318 (1942).



primary reaction is that of formaldehyde with the amine or with the active hydrogen component.[8] In the present series it is suggested that the methylene compound (IX) is an intermediate, and that in the case of primary aliphatic amines the Michael addition in stage (C) is more favorable to the addition of amine, the Mannich base therefore crystallizing out, but the addition being reversible; whereas in the case of secondary amines it is considered that the rates of addition of further lawsone or of amines are comparable, the actual product therefore depending on the relative solubilities of the Mannich base and the corresponding salt of (II), the addition of lawsone to give (II) being irreversible. The suggested course of reaction is shown.

I would like to express my indebtedness to Professor Louis F. Fieser for his interest and advice during the course of this investigation.

Experimental

All compounds for which analyses are quoted are new. M. p.'s are corrected. Products were dried at 80° in a vacuum over phosphorus pentoxide before analysis.

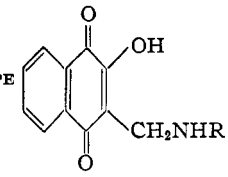
Preparation of Mannich Bases from Lawsone.—Lawsone and the appropriate amine (1.1 molecular equivalents) were dissolved in sufficient hot alcohol to keep the amine salt of lawsone in solution at room temperature (25–30°), and the mixture was filtered and allowed to cool. The aldehyde (1.2 molecular equivalents, 37% formalin solution being used for formaldehyde) was then added with shaking and the mixture set aside. With formaldehyde initial separation of product usually occurred within the hour and the product could be isolated after three hours, washed with a little alcohol, and then with ether, in which, owing to their zwitterionic nature, the products were almost insoluble. With the other aldehydes it was usually necessary to leave the mixture for twenty-four hours. With the lower homologs recrystallization from alcohol was used for purification, but the higher homologs decomposed under these conditions. They were therefore purified by stirring a suspension of the product in warm (50–60°) dilute hydrochloric acid for *ca.* fifteen minutes, by which time complete conversion to yellow hydrochloride had occurred. This was isolated, dissolved in hot alcohol, and filtered. Addition of a large volume of water to the filtrate reprecipitated the free base, but where necessary the hydrochloride could be isolated on cooling and further recrystallized. The Mannich bases obtained are summarized in Tables I–III. In general the hydrochlorides were not characterized.

Deviations from the Mannich Reaction. A. Formation of Salts of (II).—By applying the conditions described above to certain secondary amines only salts of (II) were obtained. These on treatment with hydrochloric acid gave (II) immediately. Some of the bis-salts derived from secondary amines dissociated to mono-salts on recrystallization. The products obtained with various amines were as follows:

Di-*n*-butylamine.—Red-brown bis-salt obtained on vacuum concentration of the mother liquors; **m. p. 110–111°** (dec.). Calcd. for $C_{21}H_{12}O_6 \cdot 2C_8H_{19}N$: N, 4.53. Found: N, 4.36. Leffler and Hathaway stated[9] that a salt was formed in this case, but did not isolate the product.

TABLE I

EXPERIMENTS WITH FORMALDEHYDE LEADING TO COMPOUNDS OF THE TYPE

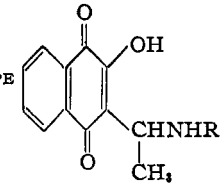


Amine, RNH_2	Yield, %	Method of purification	Crystals, orange	Cor. m. p., °C. (all with dec.)	Molecular formulas	Analyses, % Calcd.	Found
n-$C_8H_{17}NH_2$	73	[a]	Leaflets	145	$C_{19}H_{25}O_3N$	C, 72.35	72.01
						H, 7.99	8.05
n-$C_{12}H_{25}NH_2$	89	[a] or [b]	Leaflets[c]	135	$C_{23}H_{33}O_3N$	C, 74.38	74.58
						H, 8.89	8.69
n-$C_{14}H_{29}NH_2$	90	[b]	Leaflets	133	$C_{25}H_{37}O_3N$	N, 3.51	3.68
n-$C_{16}H_{33}NH_2$	92	[b]	Microcryst.	132	$C_{27}H_{41}O_3N$	N, 3.27	3.49
n-$C_{18}H_{37}NH_2$	75	[b]	Microcryst.[d]	131	$C_{29}H_{45}O_3N$	N, 3.08	3.26
2-Aminopyridine	93	[b]	Microcryst.	180–182	$C_{16}H_{12}O_3N_2$	C, 68.55	68.97
						H, 4.32	4.13

Methods of purification: [a] recrystallization from alcohol, [b] via the hydrochloride. [c] Hydrochloride forms yellow plates, decomposing above 200°. Calcd. for $C_{23}H_{33}O_3N \cdot HCl$: N, 3.43. Found: N, 3.47. [d] Hydrochloride forms yellow platelets, decomposing above 200°. Calcd. for $C_{29}H_{45}O_3N \cdot HCl$: N, 2.84. Found: N, 2.98.

TABLE II

EXPERIMENTS WITH ACETALDEHYDE, LEADING TO COMPOUNDS OF THE TYPE

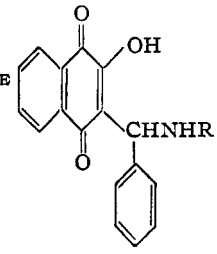


n-$C_8H_{17}NH_2$	64	[a]	Scarlet	146	$C_{20}H_{27}O_3N$	N, 4.25	4.06
n-$C_{12}H_{25}NH_2$	47	[a]	Orange-scarlet[e]	128	$C_{24}H_{35}O_3N$	N, 3.63	3.52
n-$C_{16}H_{33}NH_2$	42	[a]	Orange needlets[e]	130	$C_{28}H_{43}O_3N$	N, 3.17	3.36
2-Aminopyridine	96	[a]	Scarlet prisms	129–130	$C_{17}H_{14}O_3N_2$	N, 9.52	9.11

[e] Some tarry impurity also formed, removable by ether.

TABLE III

EXPERIMENTS WITH BENZALDEHYDE, LEADING TO COMPOUNDS OF THE TYPE



Amine RNH_2	Yield, %	Method of purification (Table I)	Description	Cor. m. p., °C. (all with dec.)	Molecular formulas	Analyses, % Calcd.	Found
n-$C_8H_{17}NH_2$	77	[a]	Scarlet prisms	155	$C_{25}H_{29}O_3N$	C, 76.67	76.78
						H, 7.47	7.36
n-$C_{10}H_{21}NH_2$	86	[a]	Scarlet	153	$C_{27}H_{33}O_3N$	N, 3.34	3.47
n-$C_{12}H_{25}NH_2$	79	[a]	Scarlet	154	$C_{29}H_{37}O_3N$	N, 3.13	3.37
n-$C_{14}H_{29}NH_2$	85	[a]	Scarlet	149	$C_{31}H_{41}O_3N$	N, 2.95	3.04
n-$C_{16}H_{33}NH_2$	82	[a]	Scarlet	146	$C_{33}H_{45}O_3N$	N, 2.78	3.00
n-$C_{18}H_{37}NH_2$	81	[b]	Orange microcryst.	135	$C_{35}H_{49}O_3N$	N, 2.64	2.55
2-Aminopyridine	96	[b]	Scarlet	192–193	$C_{22}H_{16}O_3N_2$	N, 7.87	7.55

N-Butylmonoethanolamine.—The product on recrystallization gave brick-red needles of the mono-salt of m. p. 159–160° (dec.). Calcd. for $C_{21}H_{12}O_6 \cdot C_6H_5ON$: N, 2.93. Found: N, 2.92.

Di-n-octadecylamine.—The reaction gave an oil which solidified and on recrystallization gave deep red crystals of the bis-salt of m. p. 74–76° (dec.). Calcd. for $C_{21}H_{12}O_6 \cdot 2C_{36}H_{75}N$: N, 2.00. Found: N, 2.28.

For comparative purposes salts were prepared from (II) and the following two amines by reaction of the components in ethanol.

n-**Dodecylamine.**—Bis-salt obtained as deep purple needles of m. p. 128° (dec.). Calcd. for $C_{21}H_{12}O_6 \cdot 2C_{12}H_{27}N$: N, 3.84. Found: N, 4.04.

Dimethylamine.—(II) was suspended in ethanol and dimethylamine solution added. The intense purple solution produced was concentrated to small bulk in a vacuum. On isolation of the red violet solid so obtained the color changed to red and the resultant material was far less soluble in ethanol. Treatment with cold acid gave (II) immediately, and addition of dimethylamine to an ethanolic suspension gave a purple solution of the bis-salt, the red material being the mono-salt, brick red needles from ethanol, m. p. 205° (dec.). Calcd. for $C_{21}H_{12}O_6 \cdot C_2H_7N$: N, 3.46. Found: N, 3.24.

B. Other Deviations from the Mannich Reaction.—(1) Lawsone (3.5 g., 0.02 mole) and *n*-dodecylamine hydrochloride (4.9 g., 0.022 mole) were dissolved in ethanol (100 ml.), the clear yellow solution cooled to 30°, and 37% formalin solution added (2 ml.). After a short time a small amount of yellow material separated. After standing for ninety minutes the mixture was refluxed for thirty minutes, whereupon much solid separated, which was isolated and identified by m. p. and mixed as (II) (3.1 g., 86%). (2) The reaction conducted in the usual way with benzaldehyde and piperidine gave scarlet prisms of m. p. 200° (dec.) analyzing for the bis-piperidinium salt of benzylidene-bis-lawsone. Calcd. for $C_{27}H_{16}O_6 \cdot 2C_5H_{11}N$: C, 73.27; H, 6.27. Found: C, 73.39; H, 6.04.

(3) To a solution at 25° of lawsone (1.74 g., 0.01 mole) and *p*-nitraniline (1.52 g., 0.11 mole) in ethanol was added 37% formaldehyde (1 ml.). Yellow solid soon began to separate, and after thirty minutes the mixture was boiled for five minutes and filtered hot. The yellow residue of m. p. 248–250° was identified as (II) (1.7 g., 94%). The filtrate deposited yellow needles (1.2 g., 76%) of m. p. 230–232° after recrystallization from ethanol, identified as N,N′-methylene-bis-*p*-nitraniline by comparison with an authentic sample prepared according to Pulvermacher.[9]

Reaction of Mannich Bases with Acetic Acid.—The following is typical: 2-hydroxy-3-dodecylamino-1,4-naphthoquinone (1.0 g.), was warmed with 5 ml. of glacial acetic acid. On boiling, the red solution turned yellow and after a few seconds deposited a copious yellow precipitate, which was isolated and identified by m. p. and mixed m. p. as (II) (0.45 g., 90%).

Preparation of Mannich Bases from 2,5-Dihydroxy-1,4-benzoquinone.—The preparations were similar to those using lawsone, except that 2.2 molecular equivalents of amine and 2.4 of aldehyde were used. The volume of ethanol required to keep the bis-salt of the quinone in solution was much greater, *e. g.*, with *n*-octylamine 750 ml. ethanol was required per 0.01 mole of the quinone. The following amines were used:

Piperidine.—Gave a 94% yield of 2,5-dihydroxy-3,6-bis-piperidinomethyl-1,4-benzoquinone as orange yellow platelets of m. p. 225–228° (dec.), which could be recrystallized from water. The presence of two zwitterions in the molecule renders the material appreciably soluble in cold water. Calcd. for $C_{18}H_{26}O_4N_2$: N, 8.37. Found: N, 8.17. The material gave a dihydrochloride crystallizing from ethanol as yellow platelets of m. p. 200–202° (dec.). Calcd. for $C_{18}H_{26}O_4N_2 \cdot 2HCl$: N, 6.88. Found: N, 6.81.

n-**Octylamine.**—Gave a 33% yield of 2,5-dihydroxy-3,6-bis-octylaminomethyl-1,4-benzoquinone, purified *via* the hydrochloride; scarlet platelets of m. p. 151–152° (dec.). Calcd. for $C_{24}H_{42}O_4N_2$: N, 6.63. Found: N, 6.32.

Reactions of 2-Hydroxy-3-dimethylaminomethyl-1,4-naphthoquinone.—(A) On boiling with methyl iodide in methanol the material slowly went into solution, and a yellow solid was then deposited, which was isolated, recrystallized from nitrobenzene, and identified as (II).

(9) Pulvermacher, *Ber.*, **25**, 2763 (1892).

(B) To a warm solution of the Mannich base (2.3 g.) in methanol (100 ml.) was added potassium thiocyanate (1.0 g.) in aqueous methanol. A yellow precipitate was rapidly deposited, identified as (II). (C) The Mannich base (9.2 g.), malonic ester (6.4 g.) and sodium methoxide (1.6 g.) were refluxed in iso-amyl alcohol for three hours and set aside. The purple microcrystalline precipitate of sodium salt (6.5 g.) was isolated, suspended in water, acidified, and the yellow product recrystallized from nitrobenzene and identified as (II). (D) To confirm the Mannich base formulation molecular weight determinations were made, by elevation of the b. p. of ethanol. Calcd. for $C_{13}H_{13}O_3N$: mol. wt., 231.2. Found: mol. wt., 224.2.

Reductive Acetylation of (II).—One gram of (II) was boiled with glacial acetic acid (15 ml.), acetic anhydride (15 ml.), and powdered zinc. The solution rapidly became colorless, and after ninety minutes was filtered, the residue boiled with a little acetic acid and filtered, and a small amount of water added to the combined filtrates. After separation of a rather insoluble white solid, further dilution of the mother-liquors gave a small quantity of cream-colored precipitate, separating from ethanol as white crystals of m. p. 219–221°, and shown by analysis to be 3,3′-methylene-bis-1,2,4-trihydroxynaphthalene. Calcd. for $C_{21}H_{16}O_6$: C, 69.22; H, 4.43. Found: C, 69.50; H, 4.92. The less soluble material was boiled with acetic anhydride for a further four hours to ensure complete acetylation, and the 3,3′-methylene-bis-1,2,4-triacetoxynaphthalene separated on cooling as white crystals darkening above 250° and decomposing about 270°. Calcd. for $C_{33}H_{28}O_{12}$: C, 64.29; H, 4.55. Found: C, 64.17; H, 4.54.

Reaction of Lawsone with *n*-Tetradecylamine.—Lawsone (1.74 g., 0.01 mole) and *n*-tetradecylamine (2.35 g., 0.011 mole) in ethanol (50 ml.) plus a few drops of concd. hydrochloric acid were refluxed for twenty-four hours and filtered. From the filtrate there separated a violet-brown product (1.5 g.) of m. p. 87–89°. Recrystallization from ethanol removed a violet impurity, presumably a compound of Schiff base type, to give red-brown platelets of 2-tetradecylamino-1,4-naphthoquinone of m. p. 91°, identical with material obtained (see below) from naphthoquinone and *n*-tetradecylamine. Calcd. for $C_{24}H_{35}O_2N$: C, 78.00; H, 9.55. Found: C, 77.80; H, 9.51.

If the solution of lawsone and tetradecylamine were cooled after mixing red-brown crystals of the amine salt of lawsone separated, m. p. 101–102° (dec.). Calcd. for $C_{10}H_6O_3 \cdot C_{14}H_{31}N$: N, 3.63. Found: N, 3.77.

Reaction of Amines with 1,4-Naphthoquinone.—The quinone (3.3 g.) and *n*-tetradecylamine (4.3 g.) in ethanol (50 ml.) were refluxed for ten minutes. The brown product (4.2 g., m. p. 87–88°) was recrystallized from ethanol to give red brown platelets of 2-tetradecylamino-1,4-naphthoquinone of m. p. 91°. Similarly prepared were 2-dodecylamino-1,4-naphthoquinone, m. p. 90° (Calcd. for $C_{22}H_{31}O_2N$: N, 4.11. Found: N, 4.20); and 2-octadecylamino-1,4-naphthoquinone, m. p. 95–96° (Calcd. for $C_{28}H_{43}O_2N$: N, 3.29. Found: N, 3.43).

None of these materials could be induced to give the naphthoquinone oxide, or to react with formaldehyde under conditions which readily give (II) from lawsone.

Reaction of Amines with 2,3-Dichloro-1,4-Naphthoquinone.—The quinone (4.54 g.) and octylamine (5.17 g.) were refluxed in ethanol (250 ml.) for one hour and the mixture then poured into one and one-half liters of water. After coagulation an almost theoretical yield of product was collected and recrystallized from ethanol to give scarlet plates of 2-chloro-3-octylamino-1,4-naphthoquinone of m. p. 89°. Calcd. for $C_{18}H_{22}O_2NCl$: N, 4.38. Found: N, 4.48. This material (4.9 g.) in ethanol (100 ml.) and water (50 ml.) containing potash (3 g.) was refluxed for ten minutes and then cooled. The brown silky needles (3.5 g., 90%) were isolated and identified as the potassium salt of chloro-lawsone (2-hydroxy-3-chloro-1,4-naphthoquinone), into which they were converted on acidifying their deep brown aqueous solution. Attempted hydrolyses by refluxing with sodium acetate in 70% acetic

acid, or with sodium methoxide in anhydrous methanol, resulted only in recovery of starting material in high yield.

Octadecylamine gave 2-chloro-3-octadecylamino-1,4-naphthoquinone, m. p. 97–98°. Calcd. for $C_{28}H_{42}O_2NCl$: N, 3.04. Found: N, 3.21. Hydrolysis of this material took a similar course.

Summary

1. Mannich bases have been prepared from lawsone, higher primary aliphatic amines and, as the aldehyde component, formaldehyde, benzaldehyde, or acetaldehyde. Higher secondary aliphatic amines give rise to salts of methylene-bis-lawsone. A mechanism for these reactions is suggested.

2. 2,5-Dihydroxy-1,4-benzoquinone also takes part in the Mannich reaction.

3. The Mannich bases cannot be used as alkylating agents.

4. Some 3-alkylamino-1,4-naphthoquinones and their reactions are described.

5. The compounds prepared are devoid of significant antimalarial activity.

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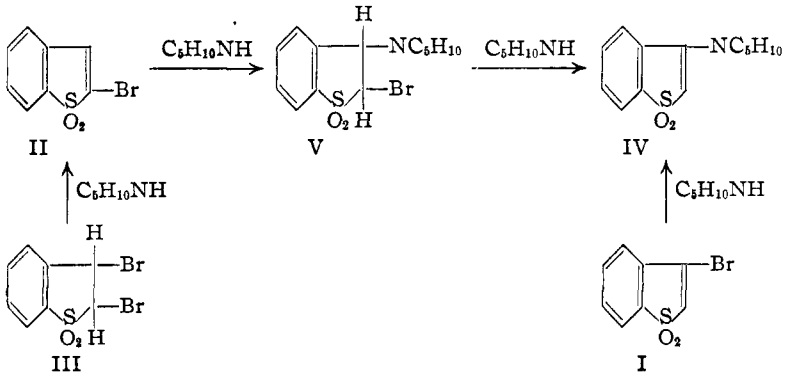
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Thianaphthene Chemistry. III. The Reaction of 2,3-Dibromo-2,3-dihydro- and 2-Bromo-thianaphthene-1-dioxides with Secondary Amines

BY F. G. BORDWELL, B. B. LAMPERT AND W. H. MCKELLIN

In a previous paper[1] the bromine atom in 3-bromothianaphthene-1-dioxide (I) was shown to be readily replaced in reactions with primary and secondary aliphatic amines or with alkoxides. It seemed of interest to test the reactivity of the isomeric 2-bromo-thianaphthene-1-dioxide (II) under similar conditions.

Thianaphthene was oxidized with hydrogen peroxide or peracetic acid in acetic acid solution to give thianaphthene-1-dioxide in greater than 90% yield. The dioxide did not react noticeably with bromine in carbon tetrachloride solution except under the influence of ultraviolet light, whereby a slow reaction occurred to give 2,3-dibromo - 2,3 - dihydrothianaphthene - 1 - dioxide (III). In hot acetic acid solution the addition was effected without illumination. The product



from the latter reaction was the same as that obtained from the reaction in carbon tetrachloride, so apparently addition of bromine to thianaphthene-1-dioxide by a free radical or ionic mechanism followed the same steric course (presumably *trans* addition). Refluxing III in benzene or alcohol solution with excess pyridine gave a quantitative yield of 2-bromothianaphthene-1-dioxide (II).

None of the bromine in I and II was released by boiling with aqueous or alcoholic silver nitrate solutions for four hours. The inertness of these bromides toward electrophilic attack by silver ion (S_N1 mechanism) is not surprising in view of the electron-attracting properties of the sulfonyl group. The addition of a small amount of sodium hydroxide to the solution of the bromide caused the rapid release of bromide ion in each case. It was found that II reacted rapidly with piperidine in hot benzene solution with the precipitation of piperidinium bromide. The bromine in II was not directly replaced by a piperidino group in this reaction, however, as was the case for I.[1] Instead, the product of the reaction was found to be 3-(1-piperidino)-thianaphthene-1-dioxide (IV), identical with the product obtained from the reaction of I with piperidine. Morpholine reacted with II in an analogous manner to give 3-(N-morpholino)-thianaphthene-1-dioxide, identical with the product obtained from I and morpholine. Similarly sodium methoxide in methyl alcohol solution gave 3-methoxythianaphthene-1-dioxide. Diethylamine did not appear to react under similar conditions, II being recovered for the most part from the reaction mixture (I reacts readily with diethylamine[1]). It seemed likely that the reaction of II with piperidine, morpholine and sodium methoxide proceeded by addition of the amine or alcohol to the 2,3-double bond to give an addition product (V) followed by dehydrobromination to IV, as shown for piperidine ($C_5H_{10}NH$).

Further investigation showed that V, as well as IV, was present in reaction mixtures in which

(1) Bordwell and Albisetti, THIS JOURNAL, 70, 1558 (1948); for paper II see, *ibid.*, 70, 1955 (1948).