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Naphthoquinone Antimalarials. II. Correlation of Structure and Activity Against *P. lophurae* in Ducks[1]

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The assays for suppressive activity against *P. lophurae* in ducks discussed in this paper were conducted under the direction of one of us, Richardson, and are reported in the CMR monograph[2] (F-1 procedure). The other author is responsible for the analysis of the assay data by a scheme that departs from the practice generally followed by pharmacologists in the field.

Evaluation of Drug Activity.—The accepted method of estimating drug activity in terms of the quinine equivalent (Q) as described by Blanchard and Marshall[2] consists in either matching the dose of quinine and of the drug under assay which cause the first sharp drop in parasitemia relative to that of the untreated controls, or else matching the doses which cause a drop to roughly analogous levels. That this scheme may lead to considerable variability in the interpretation of the assays can be seen from an examination of the illustrative example cited by Blanchard and Marshall and reproduced in Fig. 1 in the form of two dose-response curves. The doses described as producing the first "definite decrease" in parasitemia for quinine bisulfate and for Drug No. 760 are 30 and 75 mg., indicated on the curves as points *a* and *a'*, whence Q = 30/75 × 59.12%[3] = 0.24. But the choice of dosage is arbitrary, and equally "sharp drops" would have been observed had the operator employed for his second doses amounts of the standard drug and of No. 760 anywhere in the ranges of 30 to 40 mg., and of 50 to 90 mg., respectively Thus the assays might have indicated quinine equivalents varying, in the extreme case, from 0.20 to 0.47. The other pair of matched doses, *b* and *b'*, fortuitously produce responses that are more nearly analogous, but they still are not exactly the same.

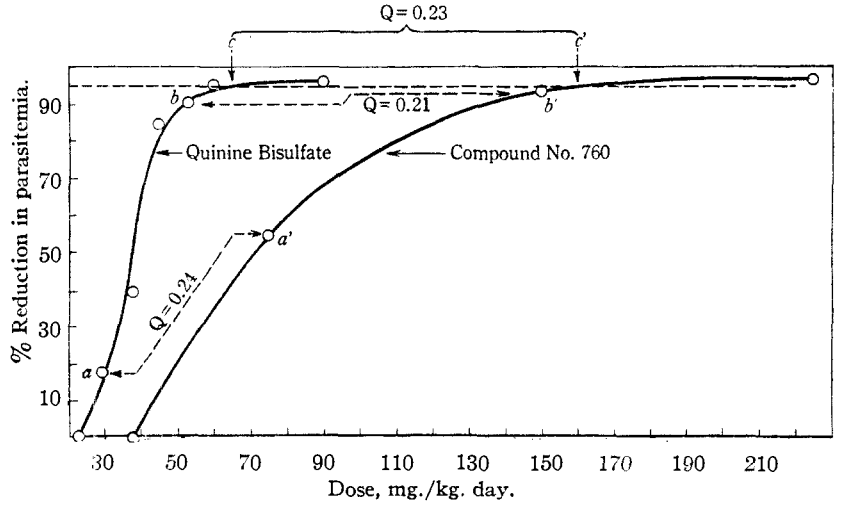


Fig. 1.—Methods of determining quinine equivalents.

The variability and uncertainty can be eliminated by the simple expedient of reading from dose response curves the dosages corresponding to any arbitrarily selected level of reduction in parasite count; for example points *c* and *c'* at the 95% level. Such ED (Effective Dose) values are objectively derived from an unambiguous definition of terms and they also have the advantage of increased reliability resulting from the graphical averaging of assays at several dosage levels. In December, 1944, the accumulated data from 46 standardization assays of quinine bisulfate were analyzed by this method, and the average ED values (for quinine bisulfate = Q) and average deviations found were as follows

$ED_{95}Q = 17.35 \pm 2.86$ (16.5 %) mg./kg./dose
$ED_{70}Q = 11.38 \pm 2.40$ (21.1 %) mg./kg./dose

The values calculated for the 70% level are thus somewhat less reproducible than the ED_{95} values and, as will be shown presently, are less generally derivable from the naphthoquinone assays. Thus the ED_{95} value, the dose (given three times a day) that is required to produce a 95% reduction in parasitemia as compared to the controls, has been employed throughout this work. The ED_{95} value derived from an assay of a given drug is corrected (to ED_{95c}) for any deviation from the standard response noted in a parallel assay of quinine bisulfate as follows

$$ED_{95c} = ED_{95} \times 17.35/ED_{95}Q$$

The quinine equivalents (free base) cited in Paper I were calculated from the formula

$$Q = 10.26\ (59.12\ \%\ \text{of}\ 17.35)/ED_{95c}$$

In the nineteen control assays of quinine bisulfate completed since the adoption of the standard value $ED_{95}Q = 17.35$ (done chiefly at New Brunswick rather than Memphis), the average doses

(1) See Paper I, Ref. 1, for acknowledgments to CMR and the Rockefeller Foundation.

(2) Wiselogle, "Survey of Antimalarial Drugs," 1946.

(3) The percentage of quinine base in the bisulfate.

are somewhat higher: $ED_{95}Q = 20.12 \pm 2.67$ and $ED_{70}Q = 12.56 \pm 1.73$. For the total 65 assays the average ratio is $ED_{70}Q/ED_{95}Q = 0.65$. In 177 individual assays of naphthoquinones (some repeats, some late results not averaged) where the results can be analyzed from dose–response curves there are 144 cases where ED_{70} and ED_{95} values can both be calculated and the over-all average ratio is 0.50 ± 0.23. In 50 instances an ED_{95} value is available where the ED_{70} figure is not, and in only 13 cases is the reverse situation encountered.

Tabulation.—The compounds listed in this paper are all 3-alkyl or aryl derivatives of 2-hydroxy-1,4-naphthoquinone or closely related substances, and each of the eighteen series into which they have been classified includes substances that possess significant activity. Some 48 other miscellaneous naphthoquinones, including a number from the Hooker collection, together with the ten quinones described in Paper XIV, have been assayed and found inactive and are not listed in the accompanying Tables. Each of these Tables except the last one lists the members of the series concerned in the order of the number of carbon atoms in the side chain, whether these atoms are in uninterrupted combination or are separated by oxygen, nitrogen, or sulfur atoms. Since the O-acyl and O-alkyl derivatives of the strongly acidic hydroxynaphthoquinones, as well as the halonaphthoquinones that may be considered as the acid chlorides of these substances, are readily convertible into the free hydroxy compounds by mild hydrolysis, these substances are all treated as derivatives of the hydroxyquinones and are entered immediately after the parent compounds. Substances with aliphatic and alicyclic side chains are listed in Tables I–X, those with unsaturated substituents of mixed types in Table XI, and those with aralkyl and aryl groups in Tables XII–XIV.

TABLE I

n-ALKYL SERIES

Side chain	M	ED_{95}	ED_{95c}
C_1	1690[a]	Inactive	
C_3	263[b]	>150 (21%)	
C_4	1709[b]	105	182
C_5	1710[b]	67	116
C_6	268[b]	76	
C_7	260[b]	40	
C_8	271	23, 40	36.5
C_9	2275	8.3, 11.2	7.7, 9.7
C_{10}	273	19, 22	20.4
C_{11}	1926	26, 40	37.1
C_{12}	1928	25, 30	27.8
C_{13}	1924	48	
C_{14}	2347	>60 (54%)	
C_{15}	1714	44	43
C_{16}	2348	Inactive	
C_{17}	2256	Inactive	

[a] Anderson and Newman, *J. Biol. Chem.*, **103**, 197, 405 (1933). [b] Hooker, THIS JOURNAL, **58**, 1163 (1936).

Compounds with side chains containing oxygen, halogen and nitrogen, respectively, appear in the next three Tables, and Table XVIII lists compounds closely related to substances of established activity or conceivably convertible into such substances in the organism. The previously known compounds that have been assayed are identified by reference notes; the reference letters appear as superscripts to the M-numbers. New compounds that were prepared for special studies or for characterization but not assayed are not listed here but are described (and coded) in the synthesis papers.

TABLE II

ISOALKYL SERIES

Side chain	M	ED_{95}	ED_{95c}
C_3	264[a]	(175)	
C_4	1706[b]	Inactive	
C_5	1523[c]	50, 71	72, 64
Acetate	1707	Weak	
Propionate	2215	>80 (77%)	
Hydroq. diacetate	1708	Feeble	
Methyl ether	1720	Inactive	
Hydroq. triacetate	1721	Inactive	
Chloride	1923	Inactive	
C_6	1711	70–80	
C_7	1929	17.7	16.1
C_8	287	19, 7, 18	16.4
C_9	2284	7.9, 10.5	8.1, 9.3
C_{10}	300	11	9.8
C_{11}	2287	15	13.3

[a] Fieser, Hartwell and Seligman, THIS JOURNAL, **58**, 1223 (1936). [b] Hooker, *ibid.*, **58**, 1168 (1936). [c] Monti, *Gazz. chim. ital.*, **45**, 52 (1915).

Whenever the assay data permit, the antimalarial activity against *P. lophurae* in ducks is reported in terms of ED_{95} and ED_{95c} values, or of the ED_{95} value alone in case a standardization assay of quinine bisulfate was not conducted. A substance is reported as inactive if it caused no reduction in the parasite count at the highest dosage tried (usually 100 mg./kg./dose three times per day). In case the highest dose tried produced a response that was either feeble or somewhat short of a 95% reduction in parasitemia, the entry under ED_{95} reports the highest dose tried, indicates that this was not great enough to produce a 95% effect, and includes in parentheses a figure recording the percentage reduction in parasitemia produced by the compound at the dose given. This permits the comparison of weakly active compounds. In a few instances the entry indicates that the lowest dose tried destroyed more than 95% of the parasites. Unless otherwise noted, the compounds were all administered orally; a citation is made in those few instances of intramuscular administration. The activity graphs are based solely upon data referring to oral administration; uncorrected ED values are used when nothing better is available.

Definition of Series.—The graphs of Figs. 2 and 3 show that in most series of quinones

TABLE III

METHYL-*n*-ALKYL SERIES

Side chain Type		Structure	M	ED_{95}	ED_{95c}
C_5	α-CH_3	—$CHMeCH_2CH_2CH_3$	1908	> 50 (64%)	
	β-CH_3	—$CH_2CHMeCH_2CH_3$	1910	90	
C_7	α-CH_3	—$CHMeC_6H_{11}$-*n*	279	(94)	
C_8	α-CH_3	—$CHMeC_6H_{13}$-*n*	280	40	
	β-CH_3	—$CH_2CHMeC_5H_{11}$-*n*	284	6.5	
	Sodium salt			3.4	3.8
C_9	α-CH_3	—$CHMeC_7H_{15}$-*n*	314	19	34
	β-CH_3	—$CH_2CHMeC_6H_{13}$-*n*	285	6.2, 5.0	6.5, 6.0
				3.5, 2.2	3.3, 3.5
	Intramuscularly			2.0	1.8
	Sodium salt, orally			2.3	2.5
	intramusc.			< 1	<0.7
	Acetate, intramusc.		306	2.1	1.9
	Propionate, intramusc.		324	2.3	1.7
	Hydroq. triacet., intramusc.		305	1.6	1.4
	Methyl ether		307	>100 (72%)	
C_{10}	β-CH_3	—$CH_2CHMeC_7H_{15}$-*n*	313	4.5	7.8
	γ-CH_3	—$CH_2CH_2CHMeC_6H_{11}$-*n*	328	13	15
C_{11}	α-CH_3	—$CHMeC_9H_{19}$-*n*	2357[a]		
C_{12}	β-CH_3	—$CH_2CHMeC_9H_{19}$-*n*	329	20	23

[a] Synthesis by R. H. Brown to be reported later.

TABLE IV

DIMETHYL-*n*-ALKYL SERIES

Side chain Type	Structure	M	ED_{95}	ED_{95c}
C_4	—$C(CH_3)_3$	1942	93	
C_6	—$CH_2C(CH_3)_3$	1934	(80)	
C_8	—$CH_2CH_2C(CH_3)_3$	2208	22.5	27.6
	—$CHMeCHMeCH_2CH_3$	309	(59)	(53)
	—$CHMeCH_2CHMe_2$	1939	>25 (27%)	
	—$CH_2CHMeCHMe_2$	269	50	
C_7	—$CH_2CHMeCHMeC_2H_5$	310	13.9	12.6
	—$CH_2CHMeCH_2CHMe_2$	270	24	
C_8	—$CHMe(CH_2)_3CHMe_2$	1944	3.3	5.6
	—$CH_2CHMeCHMeC_6H_7$-*n*	304	>50	
	—$CH_2CH_2CHMeCHMeC_2H_5$	311	30	27
	—$CH_2CH_2CHMeCH_2CHMe_2$	283	10.5	
	Sodium salt		8.0	
C_9	—$CH_2CHMe(CH_2)_3CHMe_2$	1941	10	
C_{10}	—$CH_2CHMe(CH_2)_4CHMe_2$	333	9.0	7.7
	—$CH_2CH_2CHMe(CH_2)_3CHMe_2$	1933	12, 8	13.9
C_{11}	—$(CH_3)_2CHMe(CH_2)_3CHMe_2$	1974	14.5	12.9

having open-chain aliphate substituents the activity increases to a peak value for a C_9-group and then falls off. The results for the few α-methyl-*n*-alkyl derivatives studied would seem to indicate that α-methyl branching results in a suppression of activity, but in the dimethyl-*n*-alkyl series (Table IV) an α-methyl substituted substance (M-1944) is by far the most potent of four isomers with a C_8 side chain; thus it may be that in the α-methyl-*n*-alkyl series the peak of activity is shifted to a group of carbon content higher than C_9. Since the compounds classified as belonging to the dimethyl-*n*-alkyl series contain α-, β- and γ-methyl substituents, it is not surprising that the general relationship is only roughly discernible in the activity chart. The quinones listed in Tables IV and V are of still more diversified structural types; the data tend to show that multiple branching, particularly with groups larger than

TABLE V

OTHER BRANCHED ALKYLS

Side chain Type	Structure	M	ED_{95}	ED_{95c}
C_7	—$(CH_2)_2CHEt_2$	286	>25 (73%)	
	—$CHEtCH_2CHMe_2$	1950	>90 (55%)	
C_8	—$CH_2CHEtC_4H_9$-*n*	282	20	
	—$CH_2CHEtCH_2CHMe_2$	1940	(38)	
	—$CH_2CH_2CHPr_2$	294	Inactive	
C_9	—$CH_2CH_2CHEtC_4H_9$-*n*	281	(90)	
	—$CH_2CHEtCHMeC_3H_7$-*n*	301	35	34
C_{10}	—$CH_2CHEtC_6H_{13}$-*n*	296	5.0	8.7
	—$CH_2CH_2CHEtCHMeC_3H_7$-*n*	312	>40 (24%)	
C_{12}	—$CH_2CHMeCH_2CH_2CHEtC_4H_9$-*n*	298	3.0, 11.0	5.2, 10.6
C_{13}	—$(CH_2)_2CHEtCHMe$-C_6H_{13}-*n*	331	Inactive	
C_{16}	—$CH_2CH(i\text{-}Bu)(CH_2)_2CHEtBu$	342	Inactive	

methyl, detracts from the physiological potency. Other examples of the same effect are to be found in the results for substituted cyclohexylalkyl derivatives (Table VI).

The Tables include several series in which a cycloalkyl group is separated from the quinonoid nucleus by a methylene chain of increasing length. The cyclohexylalkyl series, which appears representative and has been explored more fully than the others, is characterized by an activity chart of the usual pattern (Fig. 3) but with a shift in the peak of activity from a C_9 to a C_{10}-C_{11} side chain. Extrapolation of the curve shows that if 2-hydroxy - 3 - cyclohexyl - 1,4 - naphthoquinone (M-266) constituted the first member of this series it would possess only feeble activity (ED_{95}70). Actually M-266 is distinctly more potent (ED_{95c} 8.0) than any of the members of the cyclohexylalkyl series and it is regarded as belonging to the special group of compounds (Table X) endowed with particularly high potency associated with the presence of an alicyclic ring joined directly to the quinonoid nucleus; even the lower members of this series are unusually active, and the higher members include the most potent of all the naphthoquinones examined.

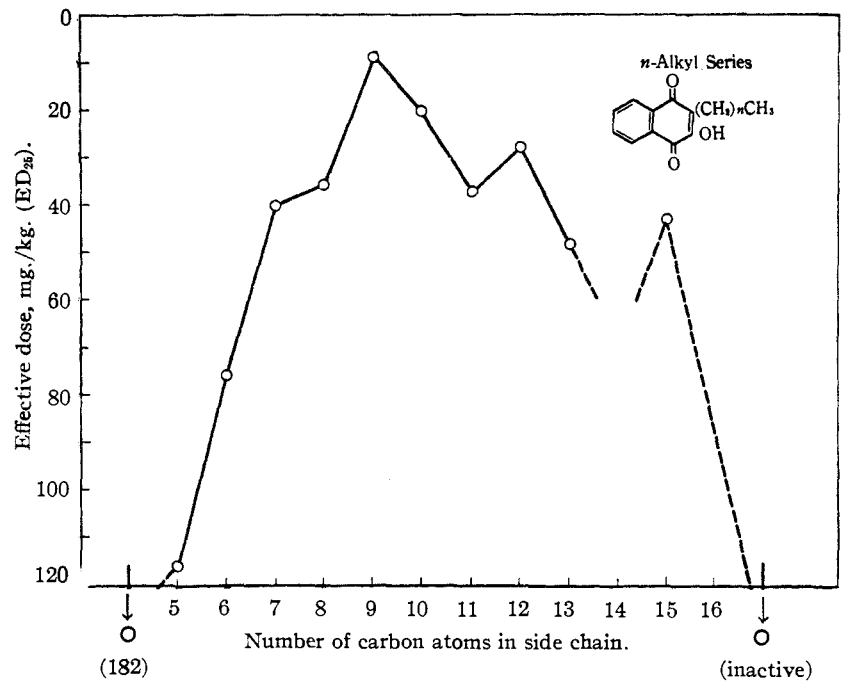


Fig. 2.—Relationship of antimalarial activity to length of side chain in the *n*-alkyl series.

TABLE VI

CYCLOHEXYLALKYL SERIES

Type	Side chain Structure	M	ED_{95}	ED_{95c}
C_7	$-CH_2C_6H_{11}$	1914	55	
C_8	$-CH_2CH_2C_6H_{11}$	1915	22	
	$-CH_2$-1(1-Me-cyclohexyl)	364	82	68
C_9	$-CH_2CH_2CH_2-C_6H_{11}$	1916	20, 13, 20, 19.2, 23.0	24, 22, 19, 18.5, 23.2
	Intramuscularly		6.2	5.6
	Sodium salt		5.0, 4.8	5.6, 5.0
	Acetate	1975	44	41
	Propionate[a]	2203	11.0	9.7
	Hydroq. triacetate[a]	1970	35	
	Hydroq. trisulfate[a]	1972	> 40	
	Oxime	383	Inactive	
C_{10}	$-(CH_2)_4-C_6H_{11}$	1971	10, 14	9.4, 13.5
	$-CH_2CHMeCH_2C_6H_{11}$	2243	18	17.4
	$-CH_2CH_2CHMeC_6H_{11}$	2246	52	39
	$-(CH_2)_3$(4-Me-C_6H_{10})	2204	>50 (99.9%)	
C_{11}	$-(CH_2)_6C_6H_{11}$	1956	4, 10, 8	8, 16, 7
	$-CH_2$-Menthyl	1963	>100 (30%)	
C_{16}	$-(CH_2)_9C_6H_{11}$	1953	77	

[a] Administered intramuscularly.

Optimum Size of Side Chain.—Table XIX shows the maximum activities observed in several series of quinones having hydrocarbon side chains. Except for the highly potent cycloalkyl series, the activities of the peak members are all in the range of ED_{95} 4 to 14. The dif-

TABLE VII

CYCLOPENTYLALKYL SERIES AND MISCELLANEOUS CYCLOALKYLALKYL COMPOUNDS

Type	Side chain Structure	M	ED_{95}	ED_{95c}
C_6	$-CH_2$-Cyclopentyl	1920	110	
C_7	$-(CH_2)_2$-Cyclopentyl	2321	35	33.8
C_8	$-(CH_2)_3$-Cyclopentyl	2322	19.1	17.1
C_9	$-(CH_2)_4$-Cyclopentyl	2331	18.3	16.9
	$-CH_2$-Cyclooctyl	2239	24	22.5
C_{10}	$-(CH_2)_5$-Cyclopentyl	2335	12.2	
C_{11}	Fr. naphthenic acid	1968	44	76
C_{12}	$-(CH_2)_3-C_9H_{16}$[a]	2319	< 8.7 (98%)	< 8.0
	$-CH_2-C_6H_{10}-C_6H_9$[b] (A)	407	4.9	4.6
	(B)	408	4.1	3.8
C_{17}	$-(CH_2)_{12}C_6H_9$	1936	87	

[a] 5-Perhydrohydrinyl. [b] 4′-Cyclopentylcyclohexyl: (A) m. p. 128°; (B) m. p. 182°.

TABLE VIII

DECALYLALKYL SERIES

Type	Side chain Structure	M	ED_{95}	ED_{95c}
C_{12}	$-(CH_2)_2$-β-Decalyl-*cis*	2320	4.6	5.5
	$-(CH_2)_2$-β-Decalyl-*trans*	2305	7.6, 5.7	6.6, 5.1
C_{13}	$-(CH_2)_3$-β-Decalyl-*cis*	2279	4, 5.5, 2	4, 4.4, 2
	Isomer A (130°)	2315	6.5, 2.9	5.6, 2.5
	Isomer B (120°)	2516	3.5, 3.2	3.0, 2.7
	$-(CH_2)_3$-β-Decalyl-*trans*	297	3.5, 9, 12	6, 8, 11.5
	Hydroq. triacetate, intramuscularly	2258	7.5	7.2
	Oxime	393	Inactive	
	$-(CH_2)_3$-α-Decalyl	2280	24.0	24.5
C_{14}	$-(CH_2)_3$-β-Decalyl-*trans*	2296	16.0	14.5

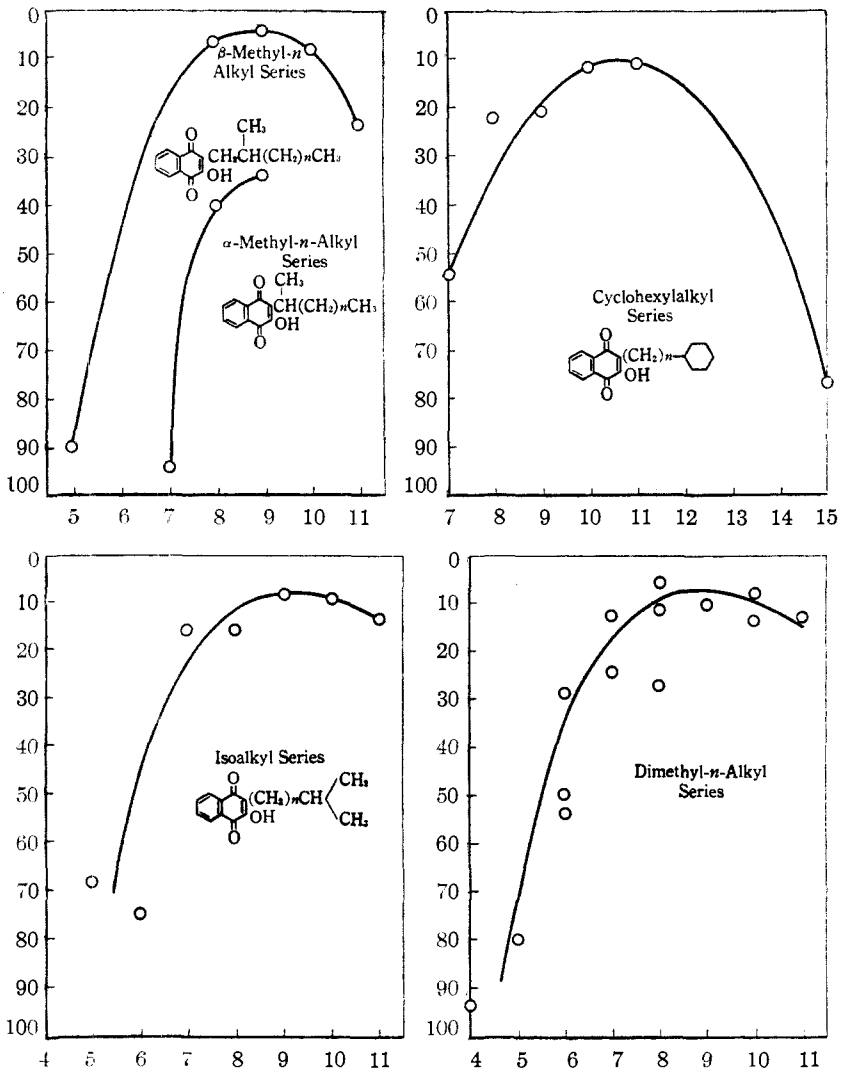


Fig. 3.—Effect of lengthening the side chain in other series (ED_{95} plotted against number of carbon atoms in the side chain).

ferent series seem to fall into distinct groups defined by the number and kind of rings present in the side chain. If no rings are present, maximum activity is reached in a C_9-group; if one alicyclic ring is present the peak is shifted to $C_{10}C_{11}$; if the side chain contains two alicyclic rings either joined or fused together the peak is displaced to C_{12}-C_{13}. A phenyl group seems to produce a still more pronounced shift in the same direction, but the present data show only that the C_{15} derivative is the most potent member assayed and is about twice as active as the C_{11} homolog. In the other two instances marked as questionable the next higher homolog was not assayed.

Influence of Configuration.—The configuration of an alicyclic ring system in the side chain is a factor of considerable importance in the determination of potency. This can be seen from the summary given in Table XX of data in Tables VII, IX and X; the configurations of the first five pairs of isomers have been established experimentally; those of the last two pairs are assumed on the basis of analogy. The *trans*-4′-cyclohexylcyclohexyl derivative M-2293 is exceptional not only in absolute potency but in being no less than thirteen times as active as the *cis* isomer.

Table VIII includes results for two pairs of β-decalylalkyl isomer mixtures that are rich, respectively, in *cis* and *trans* isomers; of these configurations the former seems to be the more favorable. A *cis*-β-decalyl group joined directly to the quinonoid nucleus (Table X) likewise gives rise to higher potency than a *trans* group.

Unsaturation.—The assay Table XI includes six instances permitting comparison of ED_{95} for unsaturated derivatives with those for the corresponding saturated compounds. In all but one case the introduction of a double bond in the 1′-, 5′-, 6′-, 8′- or 9′-position of the side chain pro-

TABLE IX

4′-CYCLOHEXYLCYCLOHEXYLALKYL SERIES

Type	Side chain Structure	M	ED_{95}	ED_{95c}
C_{13}	$—CH_2C_6H_{10}\cdot C_6H_{11}$-*cis*	384	10.5, 9.8	9.7, 8.7
	$—CH_2C_6H_{10}\cdot C_6H_{11}$-*trans*	380	2.7, 12.0	2.8, 10.7
C_{14}	$—(CH_2)_2C_6H_{10}C_6H_{11}$-*cis*	2329	45.0	
	$—(CH_2)_2C_6H_{10}C_6H_{11}$-*trans*	2330	7.7	7.1
C_{15}	$—(CH_2)_3C_6H_{10}C_6H_{11}$-*cis*	2291	16.2	14.6
	$—(CH_2)_3C_6H_{10}C_6H_{11}$-*trans*	2292	8.0	7.2

TABLE X

CYCLOALKYL SERIES

Type	Side chain Structure	M	ED_{95}	ED_{95c}
C_8	-Cyclopentyl	2326	26	26
C_9	-Cyclohexyl	266	7.0, 9.7	6.9, 9.1
C_{10}	β-Decalyl-*cis*	2328	5.5	5.0
	β-Decalyl-*trans*	2374	12.0	
C_{11}	$—C_6H_{10}\cdot C_6H_9$,[a] low m. p.	411		
	$—C_6H_{10}\cdot C_6H_9$,[a] high m. p.	412		
C_{12}	$—C_6H_{10}\cdot C_6H_{11}$[b]-*cis*	2327	7.0	9.0
	$—C_6H_{10}\cdot C_6H_{11}$[b]-*trans*	2293	0.6, 1, 0.4	0.5, 1, 0.4
	$—C_6H_{10}\cdot C_6H_5$[c]-*cis*	401	31.3	29.0
	$—C_6H_{10}\cdot C_6H_5$[c]-*trans*	400	8.0	7.4

[a] 4′-Cyclopentylcyclohexyl. [b] 4′-Cyclohexylcyclohexyl. [c] 4′-Phenylcyclohexyl.

TABLE XI

UNSATURATED SERIES

Side chain Type	Structure	M	ED_{95}	ED_{95c}
C_4	$-CH=C(CH_3)_2$	1685[a]	Inactive	
C_5	$-CH=CHCH(CH_3)_2$	1537[b]	135	235
C_7	$-CH_2CH=C(CH_3)_2$	1684[c]	>200 (87%)	
	$-CH=CH-C_5H_{11}$-*n*	1538[a]	40	68
	$-CH_2-\Delta^2$-Cyclohexenyl	827	> 80 (78%)	
C_8	$-CH=CHC_6H_5$	1715[a]	>110 (15%)	
C_9	$-(CH_2)_3-\Delta^2$-Cyclohexenyl	374	22.4, 36.0	20.2, 27.0
	$-(CH_2)_3-\Delta^3$-Cyclohexenyl	2333	47.5	44.2
	$-(CH_2)_7CH=CH_2$	2353[d]	12.5	
C_{10}	$-(CH_2)_8CH=CH_2$	289	12.0	14.3
C_{17}	-Norchaulmoogryl	1945	<100 (99%)	

[a] Hooker, THIS JOURNAL, 58, 1223 (1936). [b] Hooker, *J. Chem. Soc.*, 69, 1358 (1896). [c] Hooker, *ibid.*, 69, 1355 (1896). [d] Synthesis by R. H. Brown to be reported later.

TABLE XII

(a) ω-PHENYLALKYL SERIES AND (b) POLYARYLALKYL SERIES

Side chain Type	Structure	M	ED_{95}	ED_{95c}
	(a) ω-Phenylalkyl Series			
C_7	$-CH_2Ph$	1737[a]	>140 (43%)	
C_8	$-(CH_2)_2Ph$	1946[b]	>100 (70%)	
C_9	$-(CH_2)_3Ph$	1955[b]	65	
C_{10}	$-(CH_2)_4Ph$	2286	41	36.5
C_{11}	$-(CH_2)_5Ph$	2276	32.0	32.7
C_{16}	$-(CH_2)_9Ph$	2301	16.0	13.9
	(b) Polyarylalkyl Series			
C_{13}	$-CH(Ph)_2$	1739[c]	Inactive	
C_{14}	$-CH_2CH(Ph)_2$	2282	>100 (56%)	
C_{15}	$-CH_2CH(Ph)C_6H_4CH_3$-*p*	2274	Inactive	
C_{15}	$-CH_2CH(C_6H_4CH_3$-*p*$)_2$	2314	Inactive	
	$-CH_2CH(Ph)C_6H_3(Me)_2$-2,4	2283	Inactive	
	$-(CH_2)_2CH(Ph)C_6H_4CH_2$-*p*	2297	>100 (8%)	
C_{19}	$-C(Ph)_3$	1740[a]	Inactive	

[a] Fieser, THIS JOURNAL, 48, 3201 (1926). [b] Hooker, *ibid.*, 58, 1163 (1936). [c] Möhlau and Klopfer, *Ber.*, 32, 2146 (1899).

TABLE XIII

OTHER ARALKYL COMPOUNDS

Side chain Type	Structure	M	ED_{95}	ED_{95c}
C_9	$-(CH_2)_2C_6H_4CH_3$-*p*	2234	> 75 (17%)	
C_{10}	$-(CH_2)_2CHMePh$	2281	64	65
	$-(CH_2)_2C_6H_4Me$-*p*	1952	15.0	14.5
	$-(CH_2)_2C_6H_3Me_2$-2,4	2236	> 75 (16%)	
	$-(CH_2)_2C_6H_4Et$-*p*	2235	> 75 (84%)	
	$-CH_2CHEtPh$	2216	<100 (98%)	
C_{11}	$-(CH_2)_2C_6H_3Me_2$-2,4	2214	> 40 (62%)	
	$-(CH_2)_2C_6H_3Me_2$-2,5	2237	> 75 (68%)	
	$-(CH_2)_2C_6H_3Me_2$-3,4	2308	36	32.4
	$-CH_2CHMe(CH_2)_2Ph$	2230	Inactive	
	$-(CH_2)_3C_6H_4Et$-*p*	2209	18.5	22.9
	$-(CH_2)_2$-5-Hydrindyl	2277	> 40 (77%)	
C_{12}	$-(CH_2)_2C_6H_3Me_2$-2,4,6	2242	>100 (22%)	
	$-(CH_2)_2C_6H_4(i$-Pr$)$-*p*	2252	23.0	22.5
	$-(CH_2)_2$-β-Tetralyl	2304	> 50 (61%)	
	$-(CH_2)_2$-5-Hydrindyl	2257	36.0	34.7
C_{13}	$-(CH_2)_2C_6H_4(t$-Bu$)$-*p*	2213	37.2	35.8
	$-(CH_2)_2C_6H_3Me(i$-Pr-$)$2,5	2302	62	56
	$-(CH_2)_2$-β-Tetralyl	295	23.5, 55	40.7, 38
	$-CH_2)_2$-α-Naphthyl	2254	> 20 (18%)	
	$-(CH_2)_2$-β-Naphthyl	2253	37.0	38.0
	$-CH_2C_6H_{11}-C_6H_4$[a]-*cis*	396	95	114
C_{13}	$-CH_2C_6H_{11}\cdot C_6H_4$[a]-*trans*	395	7.5, 8.9	9.0, 8.3
C_{14}	$-(CH_2)_4$-β-Tetralyl	2295	34.0	30.8
C_{15}	$-(CH_2)_3C_6H_4Ph$-*p*	2290	>100 (7%)	
	$-(CH_2)_3C_6H_4(CH_3Ph)$-*p*	2359	(100)	
	$-(CH_2)_3-C_6H_4-C_6H_{11}$[b]-*p*	2323	56	50
C_{16}	$-(CH_2)_3C_6H_4(CH_2Ph)$-*p*	2339	20.0	
	$-(CH_2)_3$-2-Fluoryl	2272	> 80 (9%)	
C_{17}	$-(CH_2)_3$-Hydrophenanthryl[c]	2255	> 80 (11%)	
C_7-S	$-(CH_2)_2$-α-Thienyl	2285	85	76

[a] 4′-Phenylcyclohexyl. [b] Cyclohexyl. [c] 1,2,3,4-Tetrahydro-9-phenanthryl.

TABLE XIV

ARYL SERIES

Aryl group	M	ED_{95}	ED_{95c}
$-C_6H_5$	323[a]	>100 (94%)	
o-Chloro	2313	(125)	
m-Chloro	1932	Inactive	
p-Chloro	1938	45	78
o-Bromo	1937	>100 (41%)	
p-Bromo	1935	29	50
p-Iodo	2212	> 40 (37%)	
p-Fluoro	2217	> 60 (56%)	
2,4-Dichloro	1973	>100 (30%)	
2,5-Dichloro	1966	> 75 (40%)	
p-Methoxy	2288[b]	>100 (18%)	
p-Ethoxy	2298	>100 (8%)	
p-SO_3K	1901[b]	Inactive	
p-SO_2NH_2	1743	Inactive	
p-SO_2NH-2-Pyridyl	1925	Inactive	
p-$SO_2NHC(NH_2)$=NH	1919	Inactive	
o-CH_3	2317[b]	> 50 (80%)	
m-CH_3	2300	90	78
p-CH_3	1967[b]	73	127
2-Methyl-4-chloro	2225	Inactive	
2,4-$(CH_3)_2$	2307	>100 (63%)	
2-α-Naphthyl	2278	> 80 (53%)	
-β-Naphthyl	1960[b]	<100 (99%)	
3-(1,2-Naphthoquinonyl)	1731[c]	>100 (83%)	
-*p*-Xenyl	1958	> 60 (61%)	

[a] Volhard, *Ann.*, 296, 14 (1897). [b] Neunhoeffer and Weise, *Ber.*, 71, 2703 (1938). [c] Hooker and Fieser, THIS JOURNAL, 58, 1216 (1936).

duces some drop in activity; on the whole the unsaturated compounds are about 60% as active as the saturated ones. Perhaps the significant effect of the introduction of a double bond is to produce

TABLE XV

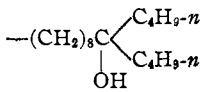
OXYGENATED SIDE CHAINS

Side chain Type	Structure	M	ED_{95}	ED_{95c}
C_3	$-CH_2CH_2COOH$	1931	Inactive	
C_4	$-CH_2C(OH)(CH_3)_2$	1685[a]	Inactive	
C_5	$-CH_2CH_2C(OH)(CH_3)_2$	1703[b]	Inactive	
	$-CH_2CH(OH)CH(CH_3)_2$	1717[c]	Inactive	
	$-CH_2CH_2CH(CH_3)CH_2OH$	1702[c]	Inactive	
	$-CH_2CH=C(CH_3)CH_2OH$	1697[c]	Inactive	
	$-CH_2CH(OH)C(OH)(CH_3)_2$	1718[b]	Inactive	
	$-CH_2COCH(CH_3)_2$	1716[d]	> 70 (13%)	
	$-(CH_2)_4COOH$	1918	>120 (10%)	
C_7	$-(CH_2)_4CH(CH_3)COOCH_3$	2233	Inactive	
C_8	$-(CH_2)_4OC_4H_9$-*n*	308	< 50 (98%)	
C_9	$-(CH_2)_8COOC_2H_5$	1917[e]	>140 (23%)	
	$-COCH_2CH_2C_6H_5$	2342[f]	Inactive	
C_{10}	$-(CH_2)_{18}OCH_3$	359	>100 (55%)	
	$-CH(C_6H_5)CH_2COCH_3$	368	Inactive	
	$-(CH_2)_3C_6H_4OCH_3$-*p*	2205	<100 (99%)	
C_{11}	$-(CH_2)_3C_6H_3(OCH_3)_2$-2,5	2364	> 80 (16%)	
	$-(CH_2)_8C(OH)(CH_3)_2$	2231	>100 (92%)	
	$-(CH_2)_4C_6H_4OCH_3$-*p*	2363	55	49
C_{12}	$-(CH_2)_5C_6H_4OCH_3$-*p*	2357	> 50 (71%), 18.0	
C_{14}	$-(CH_2)_2C_6H_4OC_6H_5$-*p*	2338	31	
C_{15}	$-(CH_2)_3$-2-Dibenzfuryl	2311	>100 (54%)	
	$-(CH_2)_2C_6H_4OPh$-*p*	2309	16.3, 8.0[h]	15.6, 7.2[h]
C_{16}	$-(CH_2)_9C_6H_4OCH_3$-*p*	2334	80	147
	$-(CH_2)_{10}OC_6H_5$	2352[g]	60	32.6
	$-(CH_2)_4C_6H_4OC_6H_5$-*p*	2361	> 80 (41%)	
C_{17}	$-(CH_2)_{10}OC_6H_4CH_3$-*p*	2368[g]	> 65 (34%)	
	$-(CH_2)_8COH(C_4H_9$-*n*$)_2$	2343	98, 16.0[h]	90, 15.0[h]
	$-(CH_2)_5C_6H_4OC_6H_5$-*p*	2345	>100 (80%)	
C_{19}	$-(CH_2)_8COH(C_5H_{11}$-*n*$)_2$	2350	80, 4.7[h]	43.3, 4.2[h]
	$-(CH_2)_6COH(C_6H_{13}$-*n*$)_2$	2376	> 60, > 20[h]	
C_{21}	$-(CH_2)_9C_6H_4OC_6H_5$-*p*	2360	64	34.7
	$-(CH_2)_8COH(C_6H_{13}$-*n*$)_2$	2367	50, 7.0[h]	44., 6.3[h]
C_{22}	$-(CH_2)_{10}OC_6H_4C_6H_5$-*p*	2370[g]	Inactive	

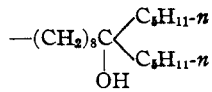
[a] Hooker, THIS JOURNAL, 58, 1223 (1936). [b] Hooker, *J. Chem. Soc.*, 61, 611 (1892). [c] Hooker, THIS JOURNAL, 58, 1181 (1936). [d] Hooker, *J. Chem. Soc.*, 69, 1355 (1896). [e] Fieser and Turner, THIS JOURNAL, 69, 2338 (1947). [f] Synthesis by D. J. Cram to be reported later. [g] Synthesis by Marvin Paulshock to be reported later. [h] Administered intramuscularly.

a displacement of the activity curve in the same direction as a phenyl substituent but to a less extent.

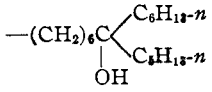
Oxygenated Side Chains.—The data of Table XV show that hydroxynaphthoquinones with various types of oxygenated side chains containing up to about twelve carbon atoms are for the most part inactive or feebly active substances. Significant activity begins to be manifested, however, when the carbon content is increased well beyond the range of optimum potency among corresponding unsubstituted compounds. Thus the most potent oxygenated compounds encountered have C_{19}–C_{21} side chains containing a tertiary hydroxyl group. Their potency is not disclosed in the usual assays by oral administration, probably because these compounds of high molecular weight are not efficiently absorbed from the gut, but assays conducted by intramuscular injection gave the following results (compounds indicated by side chains)



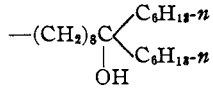
ED_{95c} 15.0(M-2343)



ED_{95c} 4.2(M-2350)



ED_{95} >20–60(M-2376)



ED_{95c} 6.3(M-2367)

When assayed by this method, M-285 (ED_{95c} 1.8) and M-1916 (ED_{95c} 5.6) proved to be 2.5–4 times as active as when given by mouth, whereas M-2350, the most potent of the four alcohols, is ten times as active when given by the injection route. It is surprising that the seemingly minor change in structure from M-2350 to the isomer M-2376 results in almost complete loss in activity; apparently a higher degree of structural specificity exists among the alcohols than in the unsubstituted compounds.

TABLE XVI

HALOGENATED SIDE CHAINS

Side chain Type	Structure	M	ED_{95}	ED_{95c}
C_4	$-CH_2CH_2CH_2CH_2Br$	2247	Inactive	
C_5	$-CH_2CH_2CCl(CH_3)_2$	1309[a]	>100 (8%)	
C_7	$-CH_2C_6H_4Cl$-*o*	2201	> 25 (6%)	
	$-CH_2C_6H_4Cl$-*p*	1738	104	
	$-CH_2C_6H_4Br$-*o*	2202	52	47.5
	$-CH_2C_6H_4Br$-*p*	2366	> 60 (54%)	
C_8	$-(CH_2)_2C_6H_4Cl$-*o*	1962	>100 (57%)	
	$-(CH_2)_2C_6H_4Cl$-*p*	2289	18.8	18.1
	$-(CH_2)_2C_6H_4Br$-*o*	1968	>100 (27%)	
	$-(CH_2)_2C_6H_4Br$-*p*	2358	55	29.8
	$-(CH_2)_2C_6H_4F$-*p*	2332	24.6	45
C_9	$-(CH_2)_3C_6H_4Cl$-*p*	2260	20.2	19.5
	$-(CH_2)_3C_6H_4Br$-*p*	2271	19.3	18.6
	$-(CH_2)_3C_6H_4F$-*p*	2244	60	57
	$-(CH_2)_3C_6H_4I$-*p*	2373	28	25
	$-(CH_2)_2C_6H_3MeCl$-3,4	2310	70	63
	$-(CH_2)_3C_6H_4CF_3$-*m*	2346	(120)	
	$-(CH_2)_2-C_6H_{10}CF_3$-*m*	2365	38	
C_{10}	$-(CH_2)_{10}Br$	340	>100 (24%)	
	$-(CH_2)_3C_6H_3MeCl$-3,4	2299	38.0	32.1
C_{11}	$-(CH_2)_6C_6H_4Cl$-*p*	2340	30	
	$-(CH_2)_6C_6H_4Br$-*p*	2341	> 50 (86%)	
C_{16}	$-(CH_2)_9C_6H_4Cl$-*p*	2344	10.2	9.4
	$-(CH_2)_9C_6H_4Br$-*p*	2362	13 0	

[a] Hooker, *J. Chem. Soc.*, 61, 611 (1892).

TABLE XVII

NITROGEN-CONTAINING SIDE CHAINS

Side chain Type	Structure	M	ED_{95}	ED_{95c}
C_3	$-CH_2N(CH_3)_2$	336	>100 (16%)	
	$-CH_2NHCH_2CH_2OH$	360	>100 (8%)	
C_5	$-CH_2NHC_4H_9$-*n*	353	130	
	$-CH_2N(C_2H_5)_2$	339	Inactive	
	-Morpholinomethyl	345	Inactive	
	$-(CH_2)_4CONH_2$	2232	Inactive	
C_6	$-CH_2NHC_6H_{11}$-*n*	346	>100 (92%)	
	$-CH_2NH$-5-(5-Me-dioxanyl)	355	Inactive	
	-Piperidinomethyl	344	38	25
C_7	$-CH_2NH$-Cyclohexyl	347	>100 (63%)	
	-2-Me-piperidinomethyl	361	170	160
	-4-Me-piperidinomethyl	362	42	40
	$-(CH_2)_4CH(CH_3)CONH_2$	2240	Inactive	
	$-CH_2C_6H_4NO_2$-*p*	1954	> 75 (60%)	
C_8	$-CH_2NHCH_2C_6H_5$	363	Inactive	
C_{17}	$-(CH_2)_{11}NH_2 \cdot HCl$	341	>100 (24%)	
	$-CH_2NHC_{10}H_{21}$-*n*	354	Inactive	
	$-(CH_2)_{16}CN$	335	>100 (61%)	
C_{14}	$-(CH_2)_{10}N(C_2H_5)_2$	379	Inactive	
C_{17}	$-CH[C_6H_4N(CH_3)_2$-*p*$]_2$	1943	>100 (8%)	

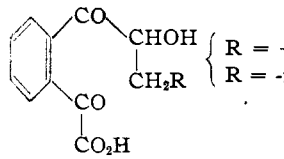
A second series of interest is that of the *p*-phenoxyphenylalkyl derivatives, exemplified by the most active member, M-2309, with the side chain $(CH_2)_3C_6H_4OC_6H_5$; this substance seems to be better absorbed than the alcohols, for it is only twice as potent when given intramuscularly (ED_{95c} 7.2) as by oral administration. The next lower homolog in this series is only half as active as M-2309 and the tetramethylene and pentamethylene homologs are only feebly active. It is very odd, therefore, that potency about half that of M-2309 appears again in the higher homolog with no less than nine methylene groups. A partial accounting for this phenomenon is to be found in Paper XXII.

Structural specificity is again evident from the fact that an *o,o'*-bridge linking together the two

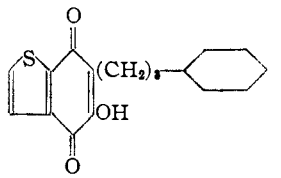
TABLE XVIII

INACTIVE RELATED COMPOUNDS

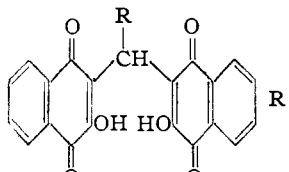
Compound	M
1,4-Naphthoquinones:	
2-Isoamyl	1743
2-Isoamyl-3-methyl	1732
2-Isoamyl-3-amino	1949
2-Hydroxy-3-isoamyl-6-methyl	2226
2-Hydroxy-3-isoamyl-7-methyl	2229
2-δ-Cyclohexylbutyl	2318
2,6-Dihydroxy-3-γ-cyclohexylpropyl	2207
2-Hydroxy-3-tetrahydrogeranyl-6-bromo	1957
2-OH-3-γ-cyclohexylpropyl-5,6,7,8-tetrahydro	2248
2-Hydroxy-3-γ-cyclohexylpropyl-7,8-benz	2324
2-Isoamyl-2,3-oxido	1900
2-Cyclohexyl-2,3-oxido	2351
2-Hydroxy-3-anilino	1904[a]
2-Hydroxy-3-*p*-chloroanilino	1905
2-Isoamylnaphthoresorcinol	348[b]
2-Phenylnaphthoresorcinol	337[c]
Alkannin	267[d]
Perezone	293[d]
Embelin	1735[e]
Rapanone	1736[e]



R = $-CH_2CH(CH_3)_2$ 1947
R = -nortetrahydrogeranyl 1948[f]



2265[g]



R = —H 1724; $-C_6H_5$ 256; $-C_6H_4Cl$-*o* 272; $-C_6H_4Cl$-*p* 276; $-C_6H_4N(CH_3)_2$-*p* 2245

[a] Zincke and Wiegand, *Ann.*, **286**, 76 (1895). [b] Soliman and West, *J. Chem. Soc.*, 53 (1944). [c] Volhard, *Ann.*, **296**, 14 (1897). [d] Mayer and Cook, "The Chemistry of Natural Coloring Matters," Reinhold Publishing Corp., New York, N. Y., 1943. [e] Synthetic, Fieser and Chamberlin, THIS JOURNAL, **70**, 71 (1948). [f] A dosage of 100 mg./kg. produced a 32% reduction in parasitemia. [g] $ED_{95} < 100$ (99%).

phenyl groups of M-2309 destroys the activity (at least as judged from oral assays). The few C_{16}-C_{22} methoxy, phenoxy, and *p*-phenylphenoxy compounds thus far examined have not exhibited high potency.

Halogenated Side Chains (Table XVI).—The introduction of an ω-bromo substituent into the side chain of 2-hydroxy-3-decyl-1,4-naphthoquinone practically abolishes the activity, but substitution in a larger alkyl group has not been investigated. An aromatically bound halo sub-

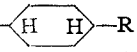
TABLE XIX

PEAK ACTIVITIES

Series	Number of rings	Side chain having maximum activity	ED_{95} of most active member
n-Alkyl	0	C_9	8.7
iso-Alkyl	0	C_9	8.7
β-Methyl-*n*-alkyl	0	C_9	4.4
Cyclohexylalkyl	1	C_{10}–C_{11}	10.5–11.4
Cyclopentylalkyl	1	C_{10}(?)	12.2
β-Decalylalkyl-*cis*	2	C_{13}	3.5
β-Decalylalkyl-*trans*	2	C_{12}	5.8
4′-Cyclohexylcyclohexyl-alkyl-*cis*	2	C_{13}	9.2
4′-Cyclohexylcyclohexyl-alkyl-*trans*	2	C_{12}	6.7
Cycloalkyl	2	C_{12}(?)	0.67
ω-Phenylalkyl	1(Bz)	C_{15}(?)	13.9

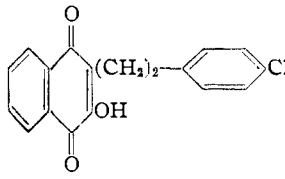
TABLE XX

ACTIVITIES OF GEOMETRICAL ISOMERS

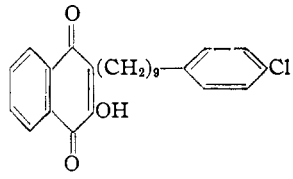
Side Chain: $-(CH_2)n-$  $-R$

R	*n*	ED_{95} *cis*/ED_{95} *trans*
Cyclohexyl	0	13.4
Cyclohexyl	1	1.3
Cyclohexyl	2	5.8
Cyclohexyl	3	1.9
Phenyl	0	3.9
Cyclopentyl	0	1.7
Cyclopentyl	1	1.2

stituent in an aralkyl side chain seems to have the effect of enhancing activity. Thus the *p*-chlorophenylethyl derivative M-2289 is slightly more potent than M-1916, whereas the unsubstituted parent compound is practically devoid of activity.



M-2289 (ED_{95c} 18.1)



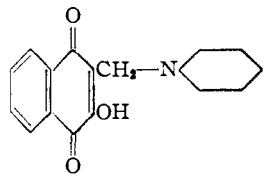
M-2344 (ED_{95c} 9.4)

The C_9 and C_{11} aralkyl homologs of M-2289 show decreased activity, but the C_{15} derivative, M-2344, exhibits twice the potency of the C_8-derivative. This resurgence of activity in a higher homolog constitutes another example of the phenomenon mentioned in the preceding section.

Although the data of Table XVI on the relative effect of ortho and para halo-substitution are not fully consistent, the burden of evidence is that the para location is the more favorable. The assays of the at most feebly active 2-hydroxy-3-aryl-1,4-naphthoquinones (Table XIV) tend to show that the order of preference is: para > ortho > meta. The assay results include two comparisons that indicate that a fluoro substituent in the benzene ring is not as favorable for activity as a chloro or bromo substituent. One comparison indicates that an iodo substituted aralkyl derivative is slightly less active (on the weight basis) than the chloro and bromo compounds. A comparison of the relative potencies of chloro and bromo derivatives is best considered in conjunction with the relative antirespiratory activities, and discussion of this point is therefore deferred to Paper XXII. It is noteworthy that hydrogenation of the aromatic ring of the *m*-trifluoromethylphenylethyl derivative results in more than three-fold increase in activity.

Nitrogen-Containing Side Chains (Table XVII).—The present results show that activity is completely lost on the introduction into a C_6–C_{11} alkyl side chain of a terminal group of the type $-NH_2$, $-N(C_2H_5)_2$, $-CN$, or $-CONH_2$. Compounds with larger side chains containing the same substituents remain to be investigated.

Surprisingly, the only nitrogen-containing quinones found to possess even moderate activity are Mannich bases containing only six or seven carbon atoms in the side chain. The most active member, M-344, is a bright red, water-soluble substance having the character of a dipolar ion.



M-344 (ED_{95c} 25)

Variations in the Naphthoquinone Nucleus (Table XVIII).—The results of such trials as have been made tend to show that little variation can be made from the standard nucleus of a 2-hydroxy-1,4-naphthoquinone without practically complete loss of activity. Thus substitution of halogen or hydroxyl at the 6-position in the aromatic ring destroys the potency exhibited by the parent compounds. The introduction of a methyl group at the 6- or 7-position in hydrolapachol results in deactivation, whereas methyl substitution in the side chain enhances the potency. The effect of these and other groups in all four available positions and the possibility of offsetting the effect of a substituent by extending the alkyl side chain is the subject of a further investigation.

The acidic quinonoid hydroxyl group appears to be essential to activity. Quinones related to hydrolapachol, M-1916 or M-1971 but having in place of hydroxyl any one of the following substituents are completely inactive: H, CH_3, NH_2, Cl, SH.

The activity of M-1916 is completely destroyed on hydrogenation of the aromatic ring. The resulting substance can be regarded as a substituted benzoquinone, and its lack of activity would suggest that the only hope of discovering active benzoquinone analogs would be through some adjustment in the size of the side chain. A preliminary assay of a thiophene isolog of M-1916 indicates that the substance possesses definite activity but

does not define the range of potency. A benzolog of the phenanthrenequinone series is completely inactive.

Transformation to Active Compounds in the Organism.—The observation that several precursors of vitamin K_1 or of 2-methyl-1,4-naphthoquinone are apparently converted efficiently into these antihemorrhagic substances in the animal body[4] suggested trial of comparable precursors of the naphthoquinone antimalarials. It appears, however, that the duck organism has relatively little power for effecting such biological transformations of orally administered materials. Thus even simple esters and hydroquinone triacetates of such active compounds as M-1916 showed at most feeble activity in oral assays. When given intramuscularly M-1916 propionate proved to be almost as active as the free hydroxy compound but the triacetate was only feebly active. In view of these findings it is hardly surprising that orally administered oxides and naphthoresorcinols showed no activity. Two of the compounds listed in Table XVIII are ketols that are readily transformed into hydroxyalkylnaphthoquinones by oxidation with copper sulfate and alkali (Paper XII) and the one of higher molecular weight showed signs of at least weak activity; this type of precursor is of interest by virtue of greatly increased water solubility.

(4) Fieser, Tishler and Sampson, *J. Biol. Chem.*, **137**, 659 (1941).

Summary

The results of this investigation are summarized in Paper I of the series.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Naphthoquinone Antimalarials. III. Diene Synthesis of 1,4-Naphthoquinones[1]

BY LOUIS F. FIESER

A reinvestigation of the reactions involved in the Diels–Alder synthesis of naphthoquinones and in the hydroxylation of the products has led to the development of shorter routes to several of the simple naphthoquinone intermediates that have been required for the synthetic program and has also provided a practical method of preparing certain hydroxyalkylnaphthoquinones that are difficultly accessible by peroxide alkylation.

In the procedure[2] heretofore usually followed the addition of butadiene to a benzoquinone is conducted in benzene, ligroin or alcohol at about 70° in a pressure vessel, the low-melting and highly soluble adduct (II) is isolated, isomerized to III, and this is oxidized with chromic acid to the naphthoquinone. It has now been found that the Diels–Alder addition can be conducted efficiently without the use of pressure equipment and at room temperature in glacial acetic acid, a solvent well adapted to use in the subsequent steps of isomerization and oxidation. The isolation of the adduct is unnecessary, for isomerization to III can be conducted by brief heating following the addition to the solution of a mineral acid and stannous chloride[3,4]; the parent substance separates in colorless needles of high purity in excellent yield. The direct oxidation of 5,8-dihydro-1,4-naphthohydroquinone (III, R = H) with chromic acid to α-naphthoquinone at first presented the difficulty that unless an excessive volume of acetic acid is employed an intermediate tar separates and does not fully redissolve. One solution is to add a dichromate–sulfuric acid mixture to the acetic acid solution of the adduct at 65–70°; the processes of isomerization and oxidation then proceed concurrently and the sparingly soluble component III never reaches a concentration high enough to cause tar formation. A still better laboratory procedure is based upon the finding that nitrous acid in acetic acid solution[5] is a specific reagent for oxidation to the dihydronaphthoquinone stage (V) and no further.[6] The reaction proceeds very readily without tar formation, and when chromic acid is subsequently added a smooth conversion to the naphthoquinone is realized.

The preparation of pure α-naphthoquinone by either procedure is far simpler than by the previous best method from α-naphthol[7] and the reactions can be applied on any scale. The compound thus becomes a practical intermediate. One use is in the preparation of 2-chloro- and 2,3-dichloro-1,4-naphthoquinone. Another application affords a better route to 2-hydroxy-1,4-naphthoquinone (VIII) than that from β-naphthol.[8] Boron fluoride (best as etherate) has been found a superior catalyst for the Thiele reaction[9] with acetic anhydride, and by a simple procedure pure 1,2,4-triacetoxynaphthalene (VII) can be prepared in quantity. A nearly quantitative conversion to pure 2-hy-

(1) See Paper I, Ref. 1, for acknowledgments to CMR and the Rockefeller Foundation.

(2) Diels and Alder, *Ber.*, **62**, 2362 (1929).

(3) Fieser, Tishler and Wendler, THIS JOURNAL, **62**, 2861 (1940).

(4) Fieser and Chang, *ibid.*, **64**, 2043 (1942).

(5) Trial of this reagent was suggested by an observation by Fieser and Peters, THIS JOURNAL, **53**, 4083, 4090 (1931).

(6) A previous search for an oxidizing agent better than chromic acid led to the discovery of the alkylating action of lead tetraacetate; Fieser and Chang.[4]

(7) Fieser, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 383.

(8) Fieser and Martin, "Organic Syntheses," **21**, 56 (1941).

(9) Thiele and Winter, *Ann.*, **311**, 347 (1900).