Developments of perhaps general application are: use of acetic acid as solvent in the diene synthesis: use of boron fluoride etherate as catalyst in the Thiele reaction, in acylations, and in the Fischer esterification of hydroxynaphthoquinone with allyl or isopropyl alcohol; use of nitrous acid in acetic acid solution for the quantitative oxidation of 5,8-dihydro-1,4-naphthohydroquinones to the dihydronaphthoquinones.

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[CONTRIBUTION FROM (a) THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY AND (b) ABBOTT LABORATORIES]

Naphthoquinone Antimalarials. IV–XI. Synthesis[1]

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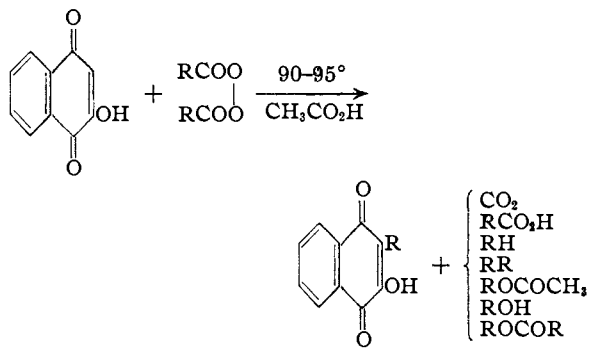
The synthesis of 3-alkyl or aralkyl derivatives of 2-hydroxy-1,4-naphthoquinone has been accomplished by condensation of the hydroxyquinone with an aldehyde and hydrogenation of the resulting 3-α-alkenyl derivative,[2] by the action of an allylic or benzyl halide on the hydroxyquinone silver salt to produce 3-derivatives either by direct C-alkylation or by rearrangement of an allylic ether,[3,4] and, in a few special cases, by condensation of the hydroxyquinone with a polyaryl carbinol.[3,5] A synthesis of long-chain 3-β-alkenyl derivatives consists in the condensation of 1,2,3,4-tetrahydroxynaphthalene with a higher allylic alcohol.[6] A novel synthesis of 2-hydroxy-3-diphenylmethyl-1,4-naphthoquinone from α-naphthoquinone and diphenyldiazomethane[7] has not been explored for generality of application because of the inaccessibility of higher diazoalkanes. Other recently developed syntheses proceed through a non-naphthalenoid intermediate. One is from a 2-alkylindanedione-1,3,[8] another is from a 3-alkyltetralone-1 by treatment either with *p*-nitrosodimethylaniline[9] or with selenium dioxide,[10] and a third involves a ring closure to a 2-alkyl-1,3-dihydroxynaphthalene and oxidation.[11] The combination of the diene synthesis and hydroxylation[12] is the subject of Paper III. The other methods mentioned have been tried or considered in the present work with but little favorable outcome. However, the great majority of the compounds sought have been readily obtainable by another method consisting in the alkylation of hydroxynaphthoquinone by a diacyl peroxide.[13] Although this and other applications of a general alkylation process[14] probably proceed through a free radical intermediate, the yields are usually adequate, pure products are readily isolated, the reaction is of wide application, and the entire synthesis from an acid through the acid chloride and peroxide is essentially a one-step process. The observations to date concerning the nature of the reaction are merely incidental and preliminary, but some of the by-products characterized are indicated in the formulation (see Paper V).



The acid by-product predominates, and considerable satisfactory starting acid is recoverable in some cases, but not in others.

One limitation in the application of the peroxide alkylation reaction to the purpose at hand is that the yields are very poor with α-branched acids and with cycloalkane carboxylic acids. In these instances it has frequently been found expedient to synthesize the next higher homolog and apply the remarkable Hooker oxidation reaction[15] whereby a methylene group is eliminated from either a saturated or unsaturated side chain. An example is in the synthesis of M-2293, illustrated in the formulas. It also is sometimes more con-

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

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

(3) Fieser, *ibid.*, **48**, 3201 (1926).

(4) Fieser, *ibid.*, **49**, 857 (1927).

(5) Möhlau and Klopfer, *Ber.*, **32**, 2146 (1899).

(6) Fieser and Gates, THIS JOURNAL, **63**, 2948 (1941).

(7) Fieser and Peters, *ibid.*, **53**, 4080 (1931).

(8) Koelsch and Byers, THIS JOURNAL, **62**, 560 (1940).

(9) Buu-Hoi and Cagniant, *Compt. rend.*, **214**, 87 (1942).

(10) Weygand and Schröder, *Ber.*, **74**, 1844 (1941).

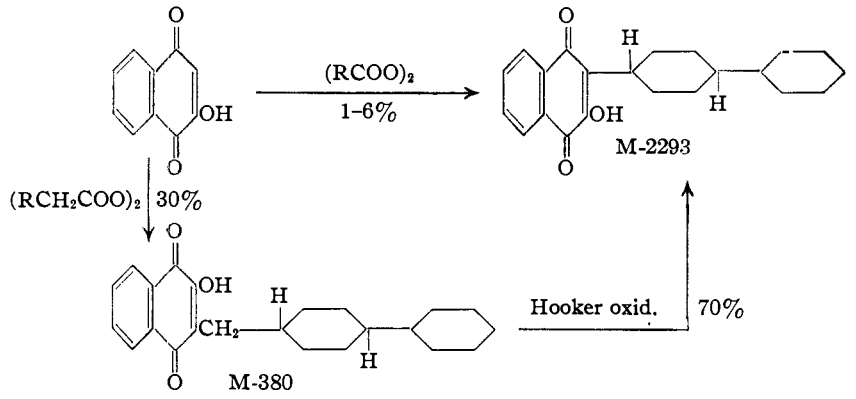
(11) Soliman and West, *J. Chem. Soc.*, 53 (1944); Soliman and Latif, *ibid.*, 55 (1944).

(12) E. Bergmann and F. Bergmann, *J. Org. Chem.*, **3**, 125 (1938).

(13) Fieser and Oxford, THIS JOURNAL, **64**, 2060 (1942).

(14) Fieser and Chang, *ibid.*, **64**, 2043 (1942); Fieser, Clapp and Daudt, *ibid.*, **64**, 2052 (1942); Fieser and Turner, *ibid.*, **69**, 2338 (1947).

(15) Hooker, THIS JOURNAL, **58**, 1168, 1174, 1179 (1936).



venient to apply one or more Hooker reactions to a product obtainable from an available acid than to prepare a batch of a lower homologous acid. Improvements in the procedure of the Hooker oxidation are reported in Paper XII.

The present series of papers reports the synthesis of all those compounds assayed or otherwise required in the course of the investigation except for a group of Mannich bases (Paper XIII) and another group of aryl-substituted compounds made by a ring-closure method (Paper XIV). Each paper lists one or more series of related compounds as classified in Paper II, and the Table numbers for quinones correspond to those of the assay Tables. Where exceptions have been made to the general classifications, the fact is noted by a cross reference. Paper IV includes a general description of the procedures of conducting the peroxide alkylation.

Acknowledgment.—The microanalyses reported in this series of papers were carried out by E. F. Shelberg and L. F. Reed of Abbott Laboratories and by Margaret M. Racich, Harvard University. Assistance in the preparation of many of the intermediates employed by the Abbott group was provided by F. E. Fisher, M. Freifelder, R. G. Hathaway, F. N. Minard and R. T. Rapala.

IV. Alkyl Side Chains (Non-cyclic, Saturated)

The combined Tables I–V list the properties, analyses and details of the preparation of all of the straight- or branched-chain 2-hydroxy-3-alkyl-1,4-naphthoquinones synthesized. A few known compounds are included either to facilitate comparison or because they were prepared for the first time by peroxide alkylation (PA); references to known compounds can be found in Paper I and are not repeated here. The Table shows that in some cases the yield of quinone obtained by alkylation was based upon peroxide, either isolated as a solid and assumed to be pure, or determined by titration, and in others was calculated from the acid chloride. Since the amount of hydroxynaphthoquinone taken is equivalent to the known or estimated amount of the dearer peroxide, the yield is calculated from the hydroxyquinone taken even though a quantity of it may have been recovered. Typical procedures used are given in the Experimental Part. The yields in the alkylation are usually in the range 30–60%, with some falling off in compounds of particularly high molecular weight. The entries in Tables III and IV show that the yield is more nearly 1–20% when the alkyl radical

TABLES I–V

3-ALKYL DERIVATIVES OF 2-HYDROXY-1,4-NAPHTHOQUINONE

K = Known. PA = Peroxide Alkylation. HO = Hooker oxidation. IHO = Improved Hooker procedure of Paper XII. P. E. = Petroleum ether. S = Sodium peroxide method. H = Hydrogen peroxide method. i = Peroxide isolated. t = Peroxide titrated.

M-	Yield, %	Acid B. p. °C.	Mm.	Formula	M. p., °C.	Prepd. by	Method	Yield, % Perox.	Yield, % Quin.[a]	Solv.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
						I. *n*-ALKYL SERIES								
263K				$C_{13}H_{12}O_3$	101–102	K. E. H.	PA	S	64	P. E.				
1709K				$C_{14}H_{14}O_3$	101–101.5									
1710K				$C_{15}H_{16}O_3$	104–105.6	H. H.	PA	S79i	36	P. E.				
268K				$C_{16}H_{18}O_3$	92–93	K. E. H.	PA	S	57	EtOH				
260				$C_{17}H_{20}O_3$	82.7–83.3									
271				$C_{18}H_{22}O_3$	88–89	K. E. H.	PA	S	36	P. E.	75.49	75.54	7.74	7.55
2275				$C_{18}H_{24}O_3$	79.5–80.5	C. H.	PA	H65i	44	MeOH	75.97	76.18	8.05	8.18
273				$C_{20}H_{26}O_3$	90–91	K. E. H.	PA	S	61	P. E.	76.40	76.35	8.34	8.10
1926				$C_{21}H_{28}O_3$	79.2–80	M. W.	PA	S60i	33		76.79	76.97	8.59	8.53
1928				$C_{22}H_{30}O_3$	93.8–94.6	W. R. V.	PA	S	26	P. E.	77.15	76.89	8.82	8.88
1924				$C_{23}H_{32}O_3$	87.2–88	M. W.	PA	S20i	70		77.49	77.73	9.05	8.63
2347				$C_{24}H_{34}O_3$	96.5–97.5	L. F. F.	IHO			EtOH	77.80	78.12	9.25	9.43
1714				$C_{28}H_{36}O_3$	89–90	M. W., M. G. E.	PA	H79t	22	MeOH	78.08	79.39	9.44	9.12
2348				$C_{26}H_{38}O_3$	100–101	L. F. F.	IHO			EtOH	78.35	78.76	9.61	9.86
2256				$C_{27}H_{40}O_3$	84.5–86.2	M. W., M. G. E.	PA	S21i	19		78.60	78.54	9.77	9.39

TABLES I–V (*Continued*)

M-	Yield, %	Acid B. p. °C.	Mm.	Formula	M. p., °C.	Prepd. by	Method	Yield, % Perox.	Yield, % Quin.[a]	Solv.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
						II. ISOALKYL SERIES								
264K				$C_{13}H_{12}O_3$	94–95	K. E. H.	PA	S	57					
1706K				$C_{14}H_{14}O_3$	132–133									
1523K[b]				$C_{15}H_{16}O_3$	93.5–94.5									
1711	49[c]	105–112	5	$C_{16}H_{18}O_3$	119.5–120	C. H.	PA	H55t	40	P. E.	74.40	74.68	7.02	7.02
1929	50[d]	Chl. 75–76	10	$C_{17}H_{20}O_3$	88.2–89.2	A. G. W.	PA	H85t	34	MeOH	74.97	75.34	7.40	7.65
287	72[e]	118	4	$C_{18}H_{22}O_3$	111.5–112.5	E. J. M., A. G. W.	PA	H88t	55	P. E.	75.49	75.51	7.74	7.77
2284				$C_{19}H_{24}O_3$	62–63	M. F.	PA	H85t	17	MeOH	75.95	75.71	8.05	8.22
300	80[e]	116–118	3	$C_{20}H_{26}O_3$	81.5–82.5[f]	E. J. M.	PA	S93t	17	MeOH	76.40	76.42	8.34	8.52
2287				$C_{21}H_{28}O_3$	73.5–74	C. H.	PA	H97t	23	MeOH	76.79	76.48	8.59	8.60
						III. METHYL *n*-ALKYL SERIES								
1908	86[g]	190–195		$C_{15}H_{16}O_3$	79.5–80.5	C. H.	PA	S40i	1.3	P. E.	73.75	73.96	6.60	6.73
1910				$C_{15}H_{16}O_3$	106–107	C. H.	PA	S64i	11	P. E.	73.75	73.53	6.60	6.56
279	81[h]	150	75	$C_{17}H_{20}O_3$	74–75	M. T. L.	PA		12	P. E.	74.96	75.03	7.35	7.35
280	57[i]	93–96	115	$C_{18}H_{22}O_3$	71–72	M. B. M.	PA		7.5	P. E.	75.49	75.47	7.74	7.54
284	76[j]	163–166	60	$C_{18}H_{22}O_3$	103–104	M. B. M.	PA		46	P. E.	75.49	75.24	7.74	7.61
314	88[k]	115–117	3	$C_{19}H_{24}O_3$	69–69.5	M. T. L.	PA	S59t	45	P. E.	75.97	75.98	8.05	7.98
285	67[l]	122–125	3	$C_{19}H_{24}O_3$	104–105	E. E. M.	PA		36	P. E.	75.97	75.92	8.05	8.00
313				$C_{20}H_{26}O_3$	97–98	E. E. M.	PA		29	MeOH	76.40	76.18	8.34	8.51
328				$C_{20}H_{26}O_3$	57–58	M. B. M.	PA	S80t	24	P. E.	76.40	76.63	8.34	8.27
329				$C_{22}H_{30}O_3$	90–90.5	M. B. M.	PA	S84t	50	MeOH	77.15	77.54	8.82	8.92
						IV. DIMETHYL *n*-ALKYL SERIES								
1942				$C_{14}H_{14}O_3$	92.4–92.6	W. R. V.	HO		62	Lig.	73.50	73.25	6.13	6.24
1934				$C_{15}H_{16}O_3$	129–131	W. R. V.	PA	S61.5i	38	Lig.	73.75	73.62	6.60	6.41
2208				$C_{16}H_{18}O_3$	122.5–123	W. R. V.	PA	S66.5i	37	MeOH	74.40	74.34	7.02	7.37
309	98[m]	111	20	$C_{16}H_{18}O_3$	86–87	K. E. H.	PA	S	21	Lig.	74.40	74.52	7.02	7.09
1939				$C_{16}H_{18}O_3$	47.5–50	H. H.	HO		68	P. E.	74.40	74.09	7.02	6.90
269	85[n]	145	79	$C_{16}H_{18}O_3$	101.5–102	K. E. H.	PA	S	62	P. E.	74.40	74.68	7.02	7.06
310				$C_{17}H_{20}O_3$	95–96	K. E. H.	PA	S	70	P. E.	74.96	75.54	7.35	7.48
270	95[o]	148	65	$C_{17}H_{20}O_3$	129–130	K. E. H., H. H.	PA	S	44	P. E.	74.96	74.89	7.35	7.30
1944				$C_{18}H_{22}O_3$	79.5–80.5	W. G. D.	HO		63	MeOH	75.49	75.87	7.74	7.92
304				$C_{18}H_{22}O_3$	78–80	M. B. M.	PA	S	7	P. E.	75.49	75.44	7.74	7.65
311				$C_{18}H_{22}O_3$	68–70	K. E. H.	PA	S	37	Lig.	75.49	75.56	7.74	7.92
283				$C_{18}H_{22}O_3$	68–69	K. E. H.	PA	S	42	P. E.	75.49	75.78	7.74	7.85
1941	58[p]	96–97	0.6	$C_{19}H_{24}O_3$	108.5–109.5	W. G. D.	PA	S86t	54	MeOH	75.97	76.27	8.05	8.36
333				$C_{20}H_{26}O_3$	97.5–98.5	M. T. L.	PA	S50t	76	MeOH	76.40	76.60	8.34	8.23
1933	35[q]	136–140	2	$C_{20}H_{26}O_3$	73.3–74.3	W. G. D.	PA	S95i	41	MeOH	76.40	76.31	8.34	8.42
1974	90[r]	121–122	1	$C_{21}H_{28}O_3$	73–74	W. G. D.	PA	H83t	49	MeOH	76.79	76.79	8.59	8.64
						V. OTHER BRANCHED ALKYLS								
286				$C_{17}H_{20}O_3$	93–94	K. E. H.	PA	S	53	P. E.	74.70	75.17	7.37	7.33
1950				$C_{17}H_{20}O_3$	55.5–57.5	H. H.	HO		82	P. E.	74.70	74.57	7.37	7.49
282	55[s]	104–105	4	$C_{18}H_{22}O_3$	122–123	K. E. H	PA	S	54		75.49	75.40	7.74	7.59
1940				$C_{18}H_{22}O_3$	130.5–132.5	H. H.	PA	S	48	Lig.	75.49	75.96	7.74	7.96
294				$C_{19}H_{24}O_3$	116–117	K. E. H.	PA	S	(13)	P. E.	75.97	75.90	8.05	8.14
281	67[t]	124	4	$C_{19}H_{24}O_3$	78–79	K. E. H.	PA	S	24	P. E.	75.97	75.98	8.05	7.98
301				$C_{19}H_{24}O_3$	126–127	K. E. H.	PA	S	30	P. E.	75.97	75.91	8.05	8.20
296				$C_{20}H_{26}O_3$	118–119	E. E. M.	PA	S	38	P. E.	76.40	76.34	8.34	8.22
312				$C_{20}H_{26}O_3$	53–54	K. E. H.	PA	S	(31)	P. E.	76.40	76.25	8.34	8.46
298				$C_{22}H_{30}O_3$	75–75.5	M. B. M.	PA	S	25	P. E.	77.16	77.34	8.83	8.89
331				$C_{23}H_{32}O_3$	55–56	K. E. H.	PA	S48t	30	Lig.	77.48	77.90	9.05	9.09
342				$C_{25}H_{36}O_3$	61–63	E. E. M.	PA	S	13	Lig.	78.08	77.91	9.44	9.76

[a] Yield based on acid chloride, not allowing for any hydroxynaphthoquinone recovered. [b] An alternate synthesis is described in Paper XI. [c] Paal and Hoffmann, *Ber.*, **23** 1498 (1890). [d] Levene and Allen, *J. Biol. Chem.*, **27** 433 (1916); present synthesis from isoamyl bromide and ethylene oxide through the nitrile (yield over-all). [e] Levene and Allen, *loc. cit.* [f] The m. p. and analysis refer to a sample prepared by Hooker oxidation, Paper XII. [g] Stiasny, *Monatsh.*, **12**, 593 (1891). [h] Karrer, *et al.*, *Helv. Chim. Acta*, **13**, 1292 (1930). [i] Kullherm, *Ann.*, **173**, 319 (1874). [j] Venable, *Ber.*, **13**, 1649 (1880). [k] Levene and Mikeska, *J. Biol. Chem.*, **84**, 571 (1929). [l] Levene and Taylor, *ibid.*, **54**, 356 (1922). [m] Chichibabin and Katznelson, see *Chem. Abst.*, **27**, 3698 (1933). [n] Huston and Agett, *J. Org. Chem.*, **6**, 123 (1941). [o] Levene and Marker, *J. Biol. Chem.*, 111, 299 (1935). [p] Peak and Robinson, *J. Chem. Soc.*, 1581 (1937). [q] Späth and Klager, *Ber.*, **67**, 859 (1934). [r] By the hydrogenation of citronellylideneacetic acid, calcd.: C, 71.95; H, 12.07. Found: C, 71.34; H, 12.22; other methods are described by Fischer and Löwenberg, *Ann.*, **475**, 183 (1929), and by Kuhn, Badstübner and Grundmann, *Ber.*, **69**, 98 (1936). [s] Keil, *Z. physiol. Chem.*, **276**, 32 (1942). [t] Keil, *ibid.*, **274**, 180 (1942).

is α-branched. Some of the α-branched compounds (M-1942, M-1938, M-1950) were made by Hooker oxidation after alkylation had been tried and found unsatisfactory.

The melting points of the quinones of the *n*-alkyl and isoalkyl series show an interesting relationship illustrated in Figs. 1 and 2.[16] In the normal series a regular alternation is observed when the side chain contains six or more carbon atoms;

(16) Hooker's best data[2,15] were used in the charts where available.

TABLE A

NEW DERIVATIVES AND INTERMEDIATES

Me = Methyl. Et = Ethyl. Pr = Propyl. Bu = Butyl. Am = Amyl. Hex = Hexyl. Mal = —$CH(CO_2C_2H_5)_2$.

M-	Compound	Formula	Method	Notes	°C.	Mm.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
				Derivatives						
273	Acetate	$C_{22}H_{18}O_4$	Ac_2O, Py, 90° (55%)	Needles	m 50–51		74.10	74.51	7.91	8.14
1523	Propionate	$C_{18}H_{22}O_4$	$(RCO)_2O$ in Py, (78%)	Yel. oil	b 174–176	1.5	71.98	71.96	6.71	6.56
	Caprylate	$C_{34}H_{38}O_4$	RCOCl in Py	Yel. oil	bath 120	1×10^{-4}	74.56	74.50	8.16	8.18
	Hydroquinone triacetate	$C_{24}H_{24}O_6$	Red. acetylat.	Prisms	m 123–125		67.73	68.21	6.50	6.72
	Methyl ether	$C_{16}H_{12}O_2$	CH_2N_2	Yel. oil	bath 56	1×10^{-7}	74.40	74.20	7.02	7.15
	hydroquinone diacet. Chloride	$C_{20}H_{24}O_5$	Red. acetylat.	From EtOH See XI	m 92–93		69.75	69.95	7.02	7.21
1711	Acetate	$C_{18}H_{20}O_4$	Ac_2O, Py, 90°	Molec. distn.	m 8–9		71.98	71.81	6.71	6.89
1929	Acetate									
287	Acetate	$C_{20}H_{24}O_4$	Ac_2O in Py, 25°	Dil. MeOH	m 45–46		73.14	73.31	7.37	7.47
285	Acetate	$C_{21}H_{26}O_4$	Ac_2O in Py, 25°	b 180–190/2 mm.	m 40–42		73.66	73.93	7.65	7.76
	Propionate	$C_{22}H_{28}O_4$	$(RCO)_2O$ in Py, 25°	$n^{24}D$ 1.5333	b 190–193	0.5	74.13	74.20	7.92	7.92
	Hydroquinone triacetate	$C_{26}H_{32}O_6$	Red. acetylat.		m 96–97		70.07	70.17	7.52	7.63
	Metbyl etber	$C_{20}H_{26}O_3$	CH_2N_2 (50%)		b 175	0.005	76.40	76.37	8.34	8.41
1933	Acetate	$C_{22}H_{28}O_4$	Ac_2O, Py 90° (57%)	Yel. oil	b 150	0.15	74.15	74.62	7.91	7.64
				Acid Intermediates						
2284	*i*-$Pr(CH_2)_6CO_2H$	$C_{10}H_{20}O_2$	Cason synth.	$n^{25}D$ 1.4318	b 93–95	0.3	69.72	69.89	11.73	11.73
	Chloride		$SOCl_2$ (91%)		b 65	0.3				
	Amide	$C_{10}H_{21}ON$		Needles	m 103.5–104.5		70.12	69.85	12.36	12.16
					m 38–39					
2287	*i*-$Pr(CH_2)_8CO_2H$	$C_{12}H_{24}O_2$	Cason syntb.	Platelets	b 140–145	3	71.95	71.90	12.07	11.82
	Me ester	$C_{13}H_{26}O_2$		$n^{25}D$ 1.4308	b 95	0.5	72.84	72.93	12.23	12.23
329	*n*-$C_9H_{19}CHMeCH_2CO_2H$	$C_{12}H_{24}O_2$	Mal. ester (83%)	$n^{23}D$ 1.4410	b 149–154	5	72.84	73.10	12.23	12.10
	Chloride		$SOCl_2$	Yield 57%	b 127–136	9				
310	$EtCHMeCHMeCH_2CO_2H$	$C_8H_{16}O_2$	Nitrile (70%)	$n^{22}D$ 1.4321	b 113–115	10	66.62	66.24	11.18	10.76
	Chloride		$SOCl_2$ (quant.)		b 100–101	65				
304	$PrCHMeCHMeCH_2CO_2H$		Mal. ester	Not isolated						
	Chloride		$SOCl_2$		b 89–91	17				
311	$EtCHMeCHMe(CH_2)_2CO_2H$	$C_9H_{18}O_2$	Mal. ester (73%)	$n^{21}D$ 1.4391	b 133–134	12	68.31	68.30	11.47	11.68
	Chloride		$SOCl_2$ (quant.)		b 117–118	60				
283	*i*-$PrCH_2CHMe(CH_2)_2CO_2H$	$C_9H_{18}O_2$	Mal. est. (95%): Grig.	$n^{23}D$ 1.4312	b 163–165	55	68.31	68.57	11.47	11.23
	Chloride		$SOCl_2$ (quant.)		b 127–129	65				
333	*i*-$PrCH(CH_2)_4CHMeCH_2CO_2H$	$C_{11}H_{22}O_2$	Mal. ester (79%)	$n^{24}D$ 1.4361	b 130–131	2	70.96	70.97	11.83	11.85
	Chloride		$SOCl_2$ (98%)		b 158–160	98				
	Amide	$C_{11}H_{23}ON$					N, 7.56	7.22		
286	$Et_2CHCH_2CH_2CO_2H$	$C_8H_{16}O_2$	See text	$n^{23}D$ 1.4320	b 104–106	7	66.62	66.73	11.19	11.00
	Chloride		$SOCl_2$ (quant.)		b 124–125	110				
1940	*i*-$PrCH_2CH_2EtCH_2CO_2H$	$C_9H_{18}O_2$	Reformatsky		b 138–140	24	68.31	68.36	11.46	11.50
	Chloride		$SOCl_2$ (72%)		b 94–96	24				
294	$Pr_2CH(CH_2)_2CO_2H$	$C_{10}H_{20}O_2$	Grig. + CO_2 (60%)	$n^{25}D$ 1.4361	b 146–147	13	69.72	70.15	11.70	11.74
	Chloride				b 118–119	60				
301	$PrCHNeCHEtCH_2CO_2H$	$C_{10}H_{18}O_2$	Grig. + CO_2 (58%)	$n^{24}D$ 1.4391	b 100–101	0.5	69.72	69.63	11.70	11.74
312	$PrCHMeCHEt(CH_2)_2CO_2H$	$C_{11}H_{22}O_2$	Mal. ester (88%)	$n^{23}D$ 1.4418	b 113–114	4	70.91	71.13	11.90	11.81
298	$BuCHEt(CH_2)_2CHMeCH_2CO_2H$	$C_{13}H_{26}O_2$	Mal. ester (90%)		b 148–149	2	72.84	73.19	12.23	12.27
	Chloride		$SOCl_2$ (92%)		b 93–94	2				
331	$HexCHMeCHEt(CH_2)_2CO_2H$	$C_{14}H_{28}O_2$	Mal. ester (91%)	$n^{23}D$ 1.4462	b 133	1	73.63	73.47	12.36	12.15
342	$BuCHEt(CH_2)_2CH(i\text{-}Bu)CH_2CO_2H$	$C_{16}H_{32}O_2$	Mal. ester (60%)	$n^{25}D$ 1.4480	b 150	1	74.94	75.45	12.58	12.54
	Chloride		$SOCl_2$ (96%)		b 124	2				
				Alkyl Malonic Esters						
329	BuCHMe—Mal[31]	$C_{18}H_{34}O_4$	From bromide (83%)		b 163–168	5	68.75	68.77	10.90	10.90
304	PrCHMeCHMe—Mal	$C_{14}H_{26}O_4$	From bromide (12%)	$n^{24}D$ 1.4350	b 130–134	10				
311	$EtCHMeCHMeCH_2$—Mal	$C_{14}H_{26}O_4$	From bromide (79%)	$n^{23}D$ 1.4335	b 152	19	65.08	65.04	10.14	10.13
283	*i*-$PrCH_2CHMeCH_2$—Mal	$C_{14}H_{26}O_4$	From bromide (62%)	$n^{23}D$ 1.4301	b 129–130	7	65.08	65.45	10.14	9.88
333	*i*-$Pr(CH_2)_4CHMe$—Mal	$C_{15}H_{30}O_4$	From bromide (80%)	$n^{23}D$ 1.4358	b 117–118	0.5	67.10	67.19	10.56	10.37
312	$PrCHMeCHEtCH_2$—Mal	$C_{15}H_{30}O_4$	From bromide (63%)	$n^{24}D$ 1.4367	b 128–129	3				
298	$BuCHEt(CH_2)_2CHMe$—Mal	$C_{18}H_{34}O_4$	From bromide (71%)	$n^{24}D$ 1.4385	b 136–141	2.5				
331	$HexCHMeCHEtCH_2$—Mal	$C_{19}H_{36}O_4$	From bromide (80%)	$n^{25}D$ 1.4401	b 152–155	4				
342	$BuCHEt(CH_2)_2CH(i\text{-}Bu)$—Mal	$C_{21}H_{40}O_4$	From bromide (31%)	$n^{24}D$ 1.4438	b 135–140	1	70.74	70.26	11.31	11.04
				Alcohols, Bromides						
294	$Pr_2CHCH_2CH_2OH$	$C_9H_{20}O$	Ethylene oxide (56%)	$n^{22}D$ 1.4350	b 84–85	9	74.94	74.30	13.98	13.14
	Bromide		PBr_3 (55%)	$n^{23}D$ 1.4428	b 129–130	60				
331	$HexCHMeCHEtCH_2OH$	$C_{12}H_{26}O$	Hydrogenol. of the malonic ester (89%)	$n^{23}D$ 1.4455	b 65	0.1	77.35	77.35	14.07	14.00
	Bromide		PBr_3 (43%)		b 77–80	0.5				

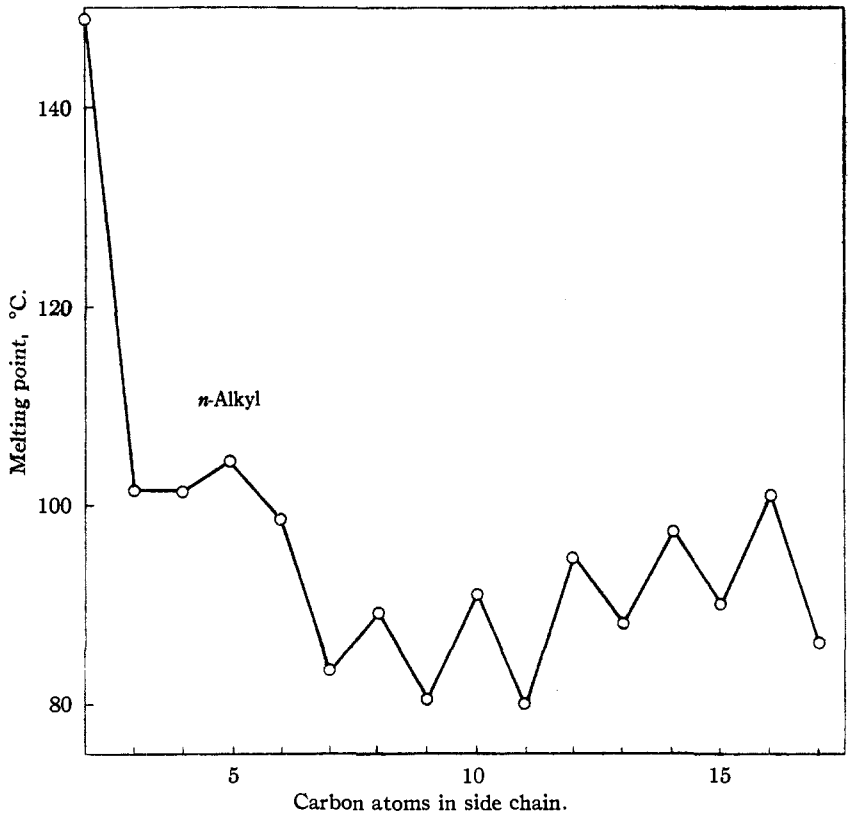


Fig. 1.—Melting points of 2-hydroxy-3-*n*-alkyl-1,4-naphthoquinones.

in the isoalkyl series a striking alternation appears from the outset (C_3). In each case the compounds with a side chain having an even number of carbon atoms attached to the acidic hydroxyquinone group melt at temperatures as much as 38° higher than the odd-carbon homologs. Among the normal fatty acids alternation is noted over the entire range of C_1 to C_{18} acids and the members of higher melting point are those with an odd-carbon alkyl group attached to carboxyl.[17]

Acknowledgment.—We are greatly indebted to Dr. Frank C. Whitmore for a generous supply of neopentyl methyl ketone and to Dr. James Cason for samples of several branched-chain keto acids.

Experimental[18]

Peroxides, Sodium Peroxide Method.—The following procedure, which is a refinement of a known method,[18,19] has given good results in a number of instances. A mixture of 100 g. of ice, 100 cc. of ice-water, and 15.6 g. (0.2 mole) of 90% sodium peroxide is stirred mechanically in a 500-cc. three-necked flask that is cooled in an ice-bath and equipped with a thermometer and dropping funnel. A solution of 0.1 mole of a given acid chloride in 50–60 cc. of pentane is then added by drops at such a rate that the temperature is maintained at 5–10°. After the addition is complete, stirring is continued for about twenty minutes longer. In some instances the peroxide separates as a solid and is collected by suction filtration and dried at a low temperature. Otherwise the layers are separated, the aqueous layer is washed with 50 cc. of pentane, and the total pentane solution is washed with ice water and an aliquot is titrated by the method of Kokatnur and Jelling.[20] Sometimes ether is added to help dissolve the peroxide and facilitate the separation of layers.

Peroxides. Hydrogen Peroxide Method.—The following procedure, which is a modification of that of von Pechmann and Vanino[21] is preferred to the sodium peroxide method by most of those experimenters who have tried both processes, particularly as applied to large-scale preparations. A solution of 0.2 mole of the acid chloride (*e. g.*, for the synthesis of M-1916, 37.7 g.) in 75 cc. of absolute ether is stirred mechanically in a 500-cc. three-necked flask that is cooled in an ice–salt-bath and equipped with a toluene thermometer and a dropping funnel. The temperature is kept at or below 0° while 14.4 cc. (0.15 mole) of ice-cold 30% hydrogen peroxide is added by portions through one of the side openings (not the funnel) in about six minutes. An ice-cold solution of 11.8 g. (0.30 mole) of sodium hydroxide (95%) in 29 cc. of water is then added slowly at such a rate that the temperature does not rise above 5° (thirty to forty minutes). Gentle stirring is continued for fifteen minutes longer and the mixture is transferred to a separatory funnel and the flask rinsed with a small volume of 20–30° petroleum ether (total solvent volume not over 125 cc.). The organic layer is washed with two 25-cc. portions of ice water, dried by adding 5 g. of Drierite to the funnel and shaking for five

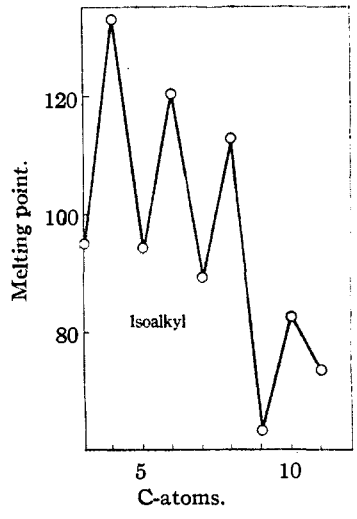


Fig. 2.—Melting points of 2-hydroxy-3-isoalkyl-1,4-naphthoquinones.

(17) For summary, see Fieser and Fieser, "Organic Chemistry," D. C. Heath and Co., Boston, Mass., 1944, pp. 166, 382.

(18) The melting points reported from the Harvard laboratory are corrected values.

(19) Gambarjan, *Ber.*, **42**, 4010 (1909).

(20) Kokatnur and Jelling, THIS JOURNAL, **63**, 1432 (1941).

(21) von Pechmann and Vanino, *Ber.*, **27**, 1510 (1894).

minutes, filtered through a plug of glass wool into a graduated receiver, kept in the cold room, and titrated.[20] Some workers (E. B.) prefer to use no more than 10% excess hydrogen peroxide in order to avoid the formation of peracid; in any case the alkali must be taken in the ratio of two moles per one of peroxide. In the preparation of some of the aliphatic peroxides, which appear to be a little less stable than those of the aralkyl series, it is advisable to keep the temperature at about −10° during the addition of the peroxide and not above −5° while the alkali is added. With some of the higher acids (*e. g.*, *trans*-4′-cyclohexylcyclohexanecarboxylic acid) it appears advantageous to use potassium hydroxide instead of sodium hydroxide; the potassium salts of the higher acids are more soluble and hence less prone to produce emulsions. A glass stirrer has always been used with the idea that a metal one might catalyze decomposition of the peroxide. In early experiments the final solution was evaporated at reduced pressure and the superficially dried solid or oily residue weighed and assumed to be pure peroxide, but this assumption is now recognized as probably unjustified. In one instance the peroxide (from cyclohexanecarboxylic acid) exploded during the evaporation. In any case it is more satisfactory to use the solution directly in the flash-distillation method described below. In the preparation of some peroxides, particularly those from the higher aralkyl acids, the peroxide often separates as a solid during the addition of alkali and is collected and either dried superficially and used directly or dried in benzene. Dipalmityl and distearyl peroxide also partially separate during the preparation and are best brought into solution by the addition of petroleum ether (*e. g.*, 100 cc. per gram of palmityl chloride). Estimated solubilities are: dipalmityl peroxide, 6.5 g./l. of ether at 15°, 17 g./l. of 20–30° petroleum ether at 20°; distearyl peroxide, 5 g./l. of petroleum at 20°.

Alkylation Procedure.—The procedure usually employed is as follows. A suspension of 17.4 g. (0.1 mole) of 2-hydroxy-1,4-naphthoquinone in 300 cc. of glacial acetic acid is heated to the maximum temperature obtainable on a steam-bath 90–95°, when the solid soon dissolves. A solution of 0.1 mole of the diacyl peroxide in ether or petroleum ether is run in very slowly through a dropping funnel with the stem extending nearly to the bottom of the flask, and a boiling stone is added to further promote rapid flash distillation of the solvent. Decomposition of the peroxide usually begins at once as evidenced by the appearance of bubbles of carbon dioxide. The best results seem to be obtained when the temperature is kept at 90° or above, a condition achieved by running the peroxide solution in very slowly (two to three hours). Heating is continued until no more gas is evolved, or for about two hours after the addition is complete, and the clear yellow reaction mixture is then worked up by one of the methods below.

If the peroxide used is a solid it can be put into the flask with the hydroxynaphthoquinone and acetic acid and the mixture cautiously warmed to 80–90°, when a vigorous evolution of carbon dioxide takes place with a mild heat effect. With large amounts it is preferable to add the solid in portions to the hot solution. In one instance a very sparingly soluble peroxide was added to the reaction mixture in solution in benzene, the solvent employed to extract it from the alkaline peroxide solution; the removal of solvent proceeded very slowly, however, and it was found better to concentrate the benzene and collect and use the crystalline peroxide.

(a) The acetic acid is removed in vacuum and the residue is taken up in ether. Some of the unchanged hydroxynaphthoquinone invariably present often can be separated at this point by filtration, and the rest is then removed by extraction from the ethereal solution with bicarbonate of soda solution. When the peroxide is of low or moderate molecular weight the acid by-product is removed at the same time, but higher acids have distribution characteristics very much like the alkylated quinone and cannot be removed by extraction. In this case separation from the acid by-product is done by crystallization or by one of the expedients given in (d).

(b) The acetic acid is removed in vacuum and the residue extracted with ligroin or petroleum ether, which leaves the bulk of the hydroxynaphthoquinone undissolved. The filtered solution is extracted with bicarbonate solution, washed with dilute acid, dried and concentrated to a point suitable for crystallization (and sometimes cooled in Dry Ice–acetone).

(c) The reaction solution is diluted with water and the mixture cooled overnight and scratched. Particularly in the aralkyl series, the alkylated quinone can be obtained directly in a crystalline condition by suitable moderate dilution. More often the precipitate is taken into ether and processed as in (a).

(d) A separation from the acid by-product sometimes can be accomplished by taking advantage of the fact that a 3-substituted hydroxynaphthoquinone remains unaffected under the conditions of Fischer esterification with methanol and sulfuric acid. After a crude reaction mixture has been so processed, water is added, the material is extracted with petroleum ether, with the addition, if required, of a not too large proportion of ether. The solution is then extracted alternately with 10% sodium hydroxide and water until the bulk of the quinone has been recovered (the quinone seems to be retained more effectively in the solvent containing the ester than in pure solvent). Another expedient that is sometimes helpful in a difficult case is to convert the product to the hydroquinone triacetate from which the acid can be separated by extraction with soda from petroleum ether; sometimes the derivative can be purified by crystallization prior to saponification and air oxidation. An expedient that may be of use where small amounts of material are concerned is to distribute the mixture between ether and dilute sodium hydroxide to which just enough sodium chloride is added to drive the quinone salt into the ether phase. The sodium salt of the acid also tends to go into the ether phase but to a somewhat lesser extent, and if careful adjustment is made some separation is often possible.

Acid Chlorides.—The procedure most generally used was to heat the acid with excess purified thionyl chloride with or without the addition of benzene or carbon tetrachloride. The other common methods were used less frequently. Usually the acid chloride was purified by vacuum distillation, but this may not always be necessary. One investigator found that undistilled sebacic half ester–half acid chloride gave a better yield of peroxide than material obtained in a distillation that was attended with considerable loss of product; another developed a distillation technique that afforded the pure ester acid chloride in 87% yield.

Explanation of Tables.—Known acids, other than common ones, utilized for the peroxide alkylations are listed in Tables I–V. The preparative procedure usually was that indicated in the reference with minor variation; the yield given is that for the last step in case more than one step was involved.

Table A lists first all new derivatives of the quinones that were prepared. The preparation of several **acetates** of the series has been accomplished in 80–90% yield by allowing a solution of the hydroxyquinone in pyridine to stand at room temperature for twenty-four hours with a large excess (20 equivalents) of acetic anhydride and pouring the solution into 2% hydrochloric acid. Acetylation also can be accomplished very effectively by use of boron fluoride etherate as catalyst (Paper III). In the preparation of a **propionate** it is sometimes advantageous to distil off the excess reagent and pyridine in vacuum and then distil the ester. Hydrolapachol **caprylate** was prepared from the acid chloride in pyridine; the product was washed free of hydroxy compound by extraction with soda from an ethereal solution and distilled in high vacuum. **Hydroquinone triacetates** were prepared by a reductive acetylation procedure as described[22] or as modified in Paper III.

(22) Fieser, "Experiments in Organic Chemistry," 2nd Ed., D. C. Heath and Co., Boston, Mass., 1941.

The next section of Table A lists the new acids that were prepared for the synthesis by peroxide alkylation of the quinones indicated, again entered by code number and Table number. The Table gives the properties and analyses of the acids and their derivatives and indicates the method used for their synthesis. A number of the acids were prepared by the malonic ester synthesis by the procedure of Adams and Kamm.[23] The malonic esters are listed in the next section of Table A; alcohol and bromide precursors not previously described are listed next. The preparation of the alcohol intermediate for M-331 was carried out by the procedure of Connor and Adkins.[24] Syntheses not readily tabulated are described in the following sections.

Cason Synthesis. (a) **Isocapric acid**, $(CH_3)_2CH(CH_2)_6CO_2H$ (for M-2284).—In accordance with the procedure of Cason,[25] the Grignard reagent from 24.3 g. of magnesium and excess isoamyl bromide was converted to the dialkylcadmium derivative and this was caused to react in benzene with 131 g. of γ-carbomethoxybutyryl chloride. Distillation of the reaction mixture afforded 122 g. (76%) of methyl 5-ketocaprate, b. p. 99.5–104° (2 mm.), and this on saponification with dilute aqueous alkali gave 103 g. of 5-ketoisocapric acid, b. p 145–150° (2.5 mm.). Reduction of the keto acid (168 g.) was accomplished by Soffer's modification[26] of the Wolff–Kishner reation with use of 85% hydrazine hydrate; a fresh portion of this reagent was added after two days of refluxing and the heating was continued for two days longer. The yield of isocapric acid (b. p. 93–95° (0.3 mm.), see Table A) was 143 g. (92%). When ethylene glycol was used as solvent and the second portion of hydrazine was omitted the yield was lower (85%, average).

(b) **Isolauric Acid**, $(CH_3)_2CH(CH_2)_8CO_2H$ (for M-2287).—The Cason procedure was followed for the reaction of the cadmium derivative from 1.2 mole each of isoheptyl bromide and magnesium and 0.64 mole of cadmium chloride with 0.96 mole of γ-carbomethoxybutyryl chloride. Fractionation of the reaction product through a 30-cm. Vigreux column gave 28 g. of dimethyl glutarate, (b. p. 90–95° (2 mm.)) and 160 g. (74%) of **methyl 5-ketoisolaurate**, b. p. 118–122° (2 mm.). The analytical sample distilled at 121° (2 mm.); d_{24} 0.9724; $n^{25}D$ 1.4408; λ max. 278–282 mμ, log ε max. 1.440.

Anal. Calcd. for $C_{13}H_{24}O_3$: C, 68.37; H, 10.60. Found: C, 68.17; H, 10.36.

5-Ketoisolauric acid, obtained by saponification of a sample of ester and distillation (b. p. 165–170° (2 mm.)), solidified and was crystallized twice from petroleum ether; the sample melted at 39.6–40°.

Anal. Calcd. for $C_{12}H_{22}O_3$: C, 67.25; H, 10.35. Found: C, 67.51; H, 10.46.

The keto ester was submitted to reduction by the Soffer procedure as in (a) and the isolauric acid collected by ether extraction and distilled; the yield of satisfactory solid material, b. p. 140–145° (3 mm.), was 80%. A sample for analysis was crystallized from petroleum ether and formed colorless platelets (see Table A for analysis and properties). The amide melts at 107.5–108°. There is no depression in melting point when isolauric acid and 5-ketoisolauric acid are mixed. Since the completion of this work Weitkamp[27] has reported the isolation from degras of a substance assigned the structure of isolauric acid on the basis of various physical properties; a close correspondence in melting point of the synthetic and natural acids and amides confirms the structure assigned.

Intermediates for M-286.—4-Ethyl-2-hexenoic acid was prepared by heating a mixture of 120 g. of 2-ethylbutyraldehyde, 240 g. of malonic acid, 480 cc. of dry pyridine, and 12 cc. of piperidine overnight on a steam-bath under reflux. The solution was poured into 2 l. of water and gave an oil that was washed with 600 cc. of 25% hydrochloric acid, washed and dried in benzene, and distilled; yield 115 g., b. p. 110–117° (7 mm.). A redistilled fraction was collected at 117° (7 mm.); $n^{22}D$ 1.4562.

Anal. Calcd. for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.82; H, 9.55.

Hydrogenation of 42.6 g. of unsaturated acid to **4-ethylcaproic acid** in 100 cc. of ethanol was conducted with 0.2 g. of platinum oxide. The saturated acid was collected at 104–106° (7 mm.) in quantitative yield (see Table A for analysis and properties).

Intermediates for M-1940.—Methyl 3-hydroxy-3-ethyl-5-methylcaproate was prepared by gradually adding a mixture of 21.4 g. of ethyl isobutyl ketone and 29 g. of methyl bromoacetate in 50 cc. of dry benzene to 15 g. of acid-treated zinc and 25 cc. of dry benzene. The mixture boiled spontaneously for thirty-five minutes and was then refluxed for eighty minutes more. The recovered reaction product distilled at 78° (1 mm.); yield 19.25 g. (57.5%).

Anal. Calcd. for $C_{10}H_{20}O_3$: C, 63.80; H, 10.71. Found: C, 63.92; H, 10.67.

A mixture of 67 g. of the above hydroxy ester and 59 g. of fused potassium bisulfate was heated with stirring for two hours at 180° and the mixture was then diluted with water and the product extracted with ether and distilled. A wide boiling range indicated that dehydration was incomplete, and so the distillate was boiled with 1 cc. of 96% sulfuric acid; the recovered product then distilled at 90–96° (21 mm.) and was hydrogenated in ethanol over Raney nickel. The filtered reaction solution was refluxed with 50 g. of potassium hydroxide for one hour and the alcohol was distilled and replaced by water and the solution acidified. Distillation of the ether-extracted material afforded 39 g. (69%) of **3-ethyl-5-methylcaproic acid**, b. p. 138–140° (24 mm.) (see Table A).

Summary

The synthesis of a considerable number of 3-substituted derivatives of 2-hydroxy-1,4-naphthoquinones is reported in a series of eight papers under the joint authorship of twenty investigators, whose specific contributions are indicated in each paper by initials in the tables. This first paper includes an introduction to the series and presents details of the synthesis of several series of quinones with saturated, non-cyclic side chains. They were prepared for the most part by peroxide alkylation of hydroxynaphthoquinone; the Hooker oxidation reaction was also employed.

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(23) Adams and Kamm, "Organic Syntheses," Coll. Vol. I, 2nd Ed., John Wiley and Sons, Inc., 1941, p. 250.

(24) Connor and Adkins, THIS JOURNAL, **54**, 4678 (1932).

(25) Cason, *ibid.*, **64**, 1106 (1942); Cason and Prout, *ibid.*, **66**, 46 (1944).

(26) Soffer, Soffer and Sberk, THIS JOURNAL, **67**, 1435 (1945).

(27) Weitkamp, *ibid.*, **67**, 447 (1945).

Naphthoquinone Antimalarials. IV–XI. Synthesis

V. Cycloalkylalkyl Series

The quinones listed in Tables VI–VIII were all initially prepared by peroxide alkylation, although in a few instances subsequent samples were made by Hooker oxidation; the melting point reported is that of the best sample available. The yield in the one alkylation involving the introduction of an α-branched radical was again notably low (14%). The Experimental Part includes an account of the characterization of by-products isolated in large-scale alkylations.

The melting points of the first six members of the cyclopentylalkyl series, counting the 2-cyclopentyl derivative (m. p. 99–100°) as the first member, show characteristic alternation and, as in the *n*- and isoalkyl series, the compounds having an odd number of carbon atoms in the side chain have the higher melting point. The first five members of the cyclohexylalkyl series, including 2-hydroxy-3-cyclohexyl-1,4-naphthoquinone (m. p. 136.5–137.5°), exhibit alternation in the opposite sense, but the sixth one, M-1956, does not conform to the relationship of the others. With this exception, the members of both series conform to the rule that the higher melting homologs are those having an odd number of methylene groups, whether the terminal alicyclic ring contains an odd or even number of carbon atoms.

Acknowledgments.—We are greatly indebted to the NDRC groups of Dr. George H. Coleman, Dr. Homer Adkins and Dr. Henry Gilman for supplies of cyclopentylvaleric acid (b. p. 120–121° (2 mm.)), *trans*-β-decalol and decalone, and methyl γ-bromocrotonate, respectively. We wish also to acknowledge the active coöperation of the Dow

TABLES VI–VIII

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

S = Sodium peroxide method. H = Hydrogen peroxide method. i = Peroxide isolated. t = Peroxide titrated. P. E. = Petroleum ether.

M-	3-Alkyl side chain	Formula	M. p., °C.	Prepd.	Yield, % Perox.	Yield, % Quin.[a]	Solv.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
			VI. CYCLOHEXYLALKYL SERIES								
1914	—CH_2-Cyclobexyl	$C_{17}H_{18}O_3$	154.5–155.5	W. G. D.	S92i	53	Lig.	75.53	75.66	6.71	6.75
1915	—$(CH_2)_2$-Cyclohexyl	$C_{18}H_{20}O_3$	111–112	W. G. D.	S81i	73	MeOH	76.03	75.82	7.09	7.09
364	—CH_2-(1-Methylcyclobexyl)	$C_{18}H_{20}O_3$	113–114	E. J. M.	S87i	46	P. E.	76.03	76.03	7.09	6.90
1916	—$(CH_2)_3$-Cyclohexyl	$C_{19}H_{22}O_3$	132.8–133.4	W. G. D.	H82t	44	Lig.	76.48	76.48	7.43	7.34
1000	—$CH_2CH(CH_3)$-Cyclohexyl	$C_{19}H_{22}O_3$	141–142	C. H.	S68i	22	MeOH	76.48	76.04	7.43	7.66
1971	—$(CH_2)_4$-Cyclohexyl	$C_{20}H_{24}O_3$	108–109	K. E. H.	S90t	37	Lig.	76.89	77.14	7.76	7.68
2262	—$CH(CH_3)CH_2CH_2$-Cyclobexyl	$C_{21}H_{24}O_3$	105.5–106.5	C. H.	H50t	14	MeOH	76.89	77.14	7.76	7.86
2243	—$CH_2CH(CH_3)CH_2$-Cyclohexyl	$C_{20}H_{24}O_3$	108–109	C. H.	H39t	67	MeOH	76.89	77.27	7.76	7.99
2246	—$CH_2CH_2CH(CH_3)$-Cyclohexyl	$C_{20}H_{24}O_3$	91–92	C. H.	H81t	67	MeOH	76.89	76.88	7.76	7.42
2204	—$(CH_2)_2$-4-Methylcyclohexyl	$C_{20}H_{24}O_3$	152–153	E. B.	H	8	EtOH	76.89	76.90	7.76	8.08
1956	—$(CH_2)_5$-Cyclohexyl	$C_{21}H_{26}O_3$	104.5–105	C. H.	S91i	21	P. E.	77.27	76.98	8.03	8.18
1963	-Menthylmethyl	$C_{21}H_{26}O_3$	193–194	F. C. C.	H	49	P. E.	77.27	77.24	8.03	8.11
2263	Isomer (isolated from alkylation)	$C_{21}H_{26}O_3$	165–167	F. C. C.			P. E.	77.27	77.31	8.03	8.21
2269	—$CH_2CH(Cyclohexyl)_2$	$C_{24}H_{30}O_3$	190.8–191.6	E. W.	H	40	Lig.	78.65	78.77	8.25	8.54
1953	—$(CH_2)_9$-Cyclohexyl	$C_{26}H_{34}O_3$	94.5–95	C. H.	S95i	20	MeOH	78.49	78.32	8.96	9.05
1001	—$CH_2CH(Cyclohexyl)$-2,4-dimethyl cyclohexyl	$C_{26}H_{34}O_3$	222–227	E. W.	H	7	Lig.	78.95	79.00	8.92	8.78
			VII, VIII. CYCLOPENTYLALKYL SERIES AND MISCELLANEOUS CYCLOALKYLALKYL COMPOUNDS								
1920	—CH_2-Cyclopentyl	$C_{16}H_{16}O_3$	159–160[b]	F. C. C.	S	(45)	MeOH	74.98	74.58	6.29	6.37
2321	—$(CH_2)_2$-Cyclopentyl	$C_{17}H_{18}O_3$	106.2–107	E. W.	H	36	Lig.	75.53	75.54	6.71	6.98
2322	—$(CH_2)_3$-Cyclopentyl	$C_{18}H_{20}O_3$	127.8–128.6	E. W.	H	22	Lig.	76.04	76.34	7.09	7.33
2331	—$(CH_2)_4$-Cyclopentyl	$C_{19}H_{22}O_3$	85.2–86.2	E. W.	H	27	Lig.	76.48	76.80	7.43	7.50
2239	—CH_2-Cyclooctyl	$C_{19}H_{22}O_3$	109–110	W. G. D.	H80i	53	MeOH	76.48	76.44	7.43	7.64
2335	—$(CH_2)_5$-Cyclopentyl	$C_{20}H_{24}O_3$	96.4–97	E. W.	H	32	Lig.	76.89	76.93	7.74	7.79
1968	From naphthenic acid fraction 2D	$C_{21}H_{26}O_3$	95–110	A. G. W.	H		MeOH	77.27	77.80	8.03	8.57
2319	—$(CH_2)_3$-5-Perhydrobydrindyl	$C_{22}H_{26}O_3$	128–133.5	C. H.	H70i	36	MeOH	78.07	77.93	7.75	7.99
407	—CH_2-4-Cyclopentylcyclohexyl (low melting)	$C_{22}H_{26}O_3$	125–128	H. E. Z.	S	6[c]	MeOH	78.07	78.62	7.75	7.71
408	—CH_2-4-Cyclopentylcyclohexyl (high melting)	$C_{22}H_{26}O_3$	181–182	H. E. Z.	S	2[c]	*i*-PrOH	78.07	77.90	7.75	7.99
1936	—$(CH_2)_{12}$-Cyclopentyl	$C_{27}H_{38}O_3$	76.8–77.8	W. G. D.	S84.5i	21	MeOH	78.98	78.98	9.33	9.46
2320	—$(CH_2)_2$-β-Decalyl-*cis* (mixt.)	$C_{22}H_{26}O_3$	117–120	A. G. W.	H85t	42	MeOH	78.07	78.23	7.75	7.98
2305	—$(CH_2)_2$-β-Decalyl-*trans* (mixt.)	$C_{22}H_{26}O_3$	110–115	A. G. W.	H85t	23	MeOH	78.07	78.01	7.75	8.07
2279	—$(CH_2)_3$-β-Decalyl-*cis* (mixt.)	$C_{23}H_{28}O_3$	117–126	A. G. W.	H93t	46.5	MeOH	78.37	78.53	8.00	8.16
2315	Isomer A	$C_{23}H_{28}O_3$	128.5–129.5	F. C. C.			MeOH	78.37	78.62	8.00	8.10
2316	Isomer B	$C_{23}H_{28}O_3$	118–119.5	F. C. C.			MeOH	78.37	78.64	8.00	8.05
297	—$(CH_2)_3$-β-Decalyl-*trans* (mixt.)	$C_{23}H_{28}O_3$	111–124	K. E. H.	S	(40)	MeOH	78.37	78.56	8.00	7.94
2280	—$(CH_2)_3$-α-Decalyl-*trans* (mixt.)	$C_{23}H_{28}O_3$	87–94	W. G. D.	H97t	22	Lig.	78.37	78.24	8.00	7.84
2296	—$(CH_2)_4$-β-Decalyl-*trans* (mixt.)	$C_{24}H_{30}O_3$	113–120	A. G. W.	H	21	Lig.	78.65	78.47	8.25	8.27

[a] Yield based on acid chloride. [b] Paper XII. [c] By alkylation with a mixture of stereoisomeric acids.

TABLE A

NEW DERIVATIVES AND INTERMEDIATES

M-	Compound (Cy = cyclo)	Formula	Method	M. p. or B. p., °C.	Mm.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
			Derivatives						
1916	Acetate	$C_{21}H_{24}O_4$	Ac_2O, Py	m 72.5–73.6		74.09	73.99	7.11	7.19
	Propionate	$C_{22}H_{26}O_4$	Refl. w. RCOCl (77%)	m 49–50		74.55	74.62	7.39	7.56
	Hydroquinone triacetate	$C_{26}H_{30}O_6$	81%	m 93.5–94		70.40	70.51	7.09	7.13
	Hydroquinone trisulfate	$C_{19}H_{21}O_{12}S_3K_3$	See text			S, 14.69	14.80		
	Oxime	$C_{19}H_{22}O_2N$	From EtOH	m 172–173		N, 4.46	4.42		
	Methyl ether	$C_{20}H_{24}O_2$	CH_2N_2 (86%), oil	b 60–65	0.0005				
	Sodium salt	$C_{19}H_{21}O_3Na$				71.23	70.69	6.61	6.95
1917	Acetate	$C_{22}H_{26}O_4$	Ac_2O, Py (75%)	m 61–63		74.54	74.50	7.40	7.66
	Hydroquinone triacetate	$C_{26}H_{32}O_6$	Red. acetylat. (60%)	m 117–117.5		70.93	71.04	7.33	7.52
	Carbethoxymethyl ether	$C_{24}H_{30}O_5$	See text	m 78.5–79		72.33	72.19	7.59	7.71
297	Acetate	$C_{25}H_{30}O_4$	Ac_2O, $(C_2H_5)_3N$ (44%)	m 80–84		76.11	76.41	7.67	7.81
	Hydroquinone triacetate		Red. acetylat.	m 117–121					
	Methyl ether	$C_{24}H_{30}O_3$	CH_2N_2 (64%), oil	Batb 170	0.0005	78.65	78.55	8.25	8.39
	Hydroq. diacet.	$C_{28}H_{36}O_5$	Red. acetylat.	m 98–101		74.31	74.57	8.01	8.18
	Oxime (crude)	$C_{28}H_{29}O_3N$	From C_6H_6	m 111/112		N, 4.04	3.28		
			Acids						
364	1-Methylcyclobexyl-CH_2CO_2H	$C_9H_{16}O_2$	Clemm. redn.,[a] $n^{30}D$ 1.4662	b 94–95	0.5	69.19	69.45	10.33	10.00
	Chloride		$SOCl_2$ (80%)	b 123–128	50				
1000	Cy-$C_6H_{11}CH_2CH(CH_3)CO_2H$	$C_{10}H_{18}O_2$	Hydrog.[c] (90%), $n^{19}D$ 1.4686	b 178–179	2	70.55	70.43	10.66	10.97
	Amide	$C_{10}H_{19}ON$		m 123–123.5		70.95	71.15	10.80	10.86
	Chloride		PCl_3; not dist.						
2243	Cy-$C_6H_{11}CH_2CH(CH_3)CH_2CO_2H$	$C_{11}H_{20}O_2$	Hydrog.[d] (88%), $n^{19}D$ 1.4630	b 150–153	1.7	71.69	71.39	10.94	11.05
	Amide	$C_{11}H_{21}ON$		m 104.5–105		72.08	71.97	11.55	11.32
	Chloride		$SOCl_2$ (91%)	b 110–111	2				
2246	Cy-$C_6H_{11}CH(CH_3)CH_2CH_2CO_2H$[b]	$C_{11}H_{20}O_2$	Hydrog.[e] (73%), $n^{29}D$ 1.4670	b 147–149	3	71.69	71.57	10.94	11.19
	Chloride		$SOCl_2$ (80%)	b 106–107	2				
2322	Cy-$C_6H_9(CH_2)_2CO_2H$	$C_9H_{16}O_2$	Arndt–Eistert (36%)[f]	b 110–115	0.5				
407,	*p*-Cyclopentylacetophenone	$C_{13}H_{16}O$	Fried.–Crafts (77%)[g]	b 140–145	2.5	82.93	82.98	8.57	8.50
408	*p*-Cyclopentylbenzoic acid	$C_{12}H_{14}O_2$	NaOBr in dioxane	m 196–198		75.76	75.65	7.42	7.51
	-phenylthioacetomorpholide	$C_{17}H_{23}ONS$	S + morpholine (75%)	m 97	98	70.53	70.32	8.01	7.90
	p-Cyclopentylphenylacetic acid	$C_{13}H_{16}O_2$	H_2SO_4–HOAc (82%)	m 66–67		76.44	76.62	7.89	7.71
	Methyl ester	$C_{14}H_{18}O_2$	From morpholide[h]	b 138–144	2	77.03	76.41	8.30	8.30
	4-Cyclopentyl-Cy-hexylacetic acid	$C_{13}H_{22}O_2$	Ni-hydrog. of ester (34%)	m 75 (range)		74.24	74.67	10.55	10.44
	Pure isomer	$C_{13}H_{22}O_2$	Fract. cryst. (text)	m 130–131		74.24	74.41	10.55	10.46
2319	γ-5-Perbydrobydrindylbutyric acid		Ni-bydrog. (86%)[i]						
	Ethyl ester	$C_{15}H_{26}O_2$		b 115	2	75.58	75.92	11.00	11.05

[a] Of 3-keto acid, Farmer and Ross, *J. Chem. Soc.*, 2365 (1925). [b] An optically active form is described by Levene and Marker, *J. Biol. Chem.*, **97**, 568 (1932). [c] Of β-phenylbutyric acid kindly supplied by Dr. H. E. Carter. [d] Aryl acid prepared according to Carter, *ibid.*, 108, 622 (1935). [e] Of 4-phenylpenten-3-oic acid, Kloetzel, THIS JOURNAL, 62, 1708 (1940). [f] Chloride, b 108–109° (7 mm.). [g] $n^{25}D$ 1.5485. [h] $n^{25}D$ 1.5230. [i] Chloride, b. p. 125–135° (3.5 mm.).

TABLE B (W. G. D.)

SYNTHESIS OF CYCLOÖCTYLACETIC ACID

No.	Compound	Formula	Method	Yield, %	M. p. or b. p., °C.	Mm.	$n^{20}D$	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1	Ethyl cycloöctanol acetate	$C_{12}H_{22}O_3$	Reformatsky	31	b 98.5–100	0.5	1.4718	67.25	67.18	10.35	10.55
2	Cycloöctanolacetic acid	$C_{10}H_{18}O_3$	Saponif. of 1	79	m 71.5–72.5			64.49	64.55	9.74	9.55
3	Ethyl cycloöctenyl acetate	$C_{12}H_{20}O_2$	1 + HCl at 90°[a]	41	b 81–83	0.7	1.4770	73.43	73.41	10.27	10.39
4	Cycloöctenylacetic acid	$C_{10}H_{16}O_2$	Saponif. of 3	87	b 126–127	0.5	1.4960	71.39	71.39	9.59	9.71
			1 + PBr_3; KOH	61	b 118–120	0.5	1.4950				
			2 + Ac_2P, Py, refl.	80	b 126–128	0.5	1.4964	71.39	71.39	9.59	9.77
	Amide	$C_{10}H_{17}ON$[b]			m 139–140			71.81	72.02	10.25	9.94
5	Cycloöctylacetic acid	$C_{10}H_{18}O_2$	See Table A					70.53	70.20	10.66	10.72

[a] Method of Natelson and Gottfried, THIS JOURNAL, 61, 971 (1939). [b] Calcd.: N, 8.38. Found: N, 8.44.

Chemical Company in providing otherwise inaccessible intermediates and of the Lucidol Corporation for carrying out the peroxide alkylation step in a large-scale preparation of material for clinical trial.

Experimental

The properties and analyses of derivatives and new intermediates are reported in Table A. Most of the acids containing a hydroaromatic group were prepared by hydrogenation of an aralkyl acid that was also used directly for the synthesis of a quinone of the series described in Paper VIII, and the preparative details are recorded there. Details concerning quinones, derivatives and intermediates that supplement the data given in the Tables are recorded in the following paragraphs.

Large-Scale Preparations

M-1916 (H. H.).—The yields recorded in Table VI represent results obtained in a group-preparation of a batch of the quinone from a total of about 2 kg. of β-

TABLE C

HYDROAROMATIC ACID MIXTURES

M-	Starting material (See Paper VIII)	Hydrog. as Me-ester, B. p., °C.	Mm.	Cat.	Yield, %	Product: Acid °C.	Mm.	M. p. or b. p. Ester °C.	Mm.	Chloride °C.	Mm.	$n^{25}D$ Acid	$n^{25}D$ Ester
2320	β-3-Tetralylpropionic acid[a]	As acid		Pt	90	m 45–60				124	0.5		
2305		132–135	0.5[b]	Ni	80	158–160	1.3	110–118	0.5[c]	142	4		1.4840
2280	γ-1-Naphtbylbutyric acid	140–141	0.7	Ni	87	153–155	0.5	120–121	1	122–123	0.9	1.4973	1.4848
2296	δ-2-ar-Tetralylvaleric acid	160	1.5[d]	Ni	80	178–180	0.5	140	1	145–147	0.5		1.4809
						m 35–60							
2204	γ-p-Tolylbutyric acid	As acid		Pt	90	b 146–148	5						
2269	β,β-Diphenylpropionic acid	Et-ester: 142–145	0.5	Ni	60	m 118–120[e]				145	0.5		
1001	β-Phenyl-β-m-xylylpropionic acid	158–162	1	Ni	46			b 112	0.5[f]	152	1.5		

[a] Freed from sulfur by treatment in soda solution with permanganate until the color persisted; the solution was clarified with sulfur dioxide and the acid recovered and esterified. [b] Newman and Zahm, THIS JOURNAL, 65, 1097 (1943); $n^{25}D$ 1.5273. [c] Compare v. Braun, *Chem. Zentr.*, 109, I, 501 (1938). [d] $n^{25}D$ 1.5200. [e] Calcd. for $C_{18}H_{26}O_2$: C, 75.58; H, 10.95. Found: C, 76.17; H, 11.09. [f] Calcd. for $C_{18}H_{32}O_2$: C, 76.83; H, 11.82. Found: C, 77.14; H, 11.35.

benzoylpropionic acid. The Clemmensen reduction was conducted by the Martin procedure with the use of sulfur-free toluene, and the over-all yield of distilled γ-phenylbutyric acid suitable for hydrogenation was 74% based on succinic anhydride used. Hydrogenation was accomplished in acetic acid in the presence of Adams catalyst at a pressure of 3 atmospheres and the acid chloride prepared by heating the acid with two moles of purified thionyl chloride on the steam-bath for one to two hours, distilling excess reagent under reduced pressure, adding a small volume of dry benzene and distilling the solvent, and then distilling the acid chloride. The peroxide preparation and the alkylation were conducted by the hydrogen peroxide procedure described in Part 1 in runs employing up to 100 g. of acid chloride. The product was isolated by method (b) and successive crops obtained by chilling the ligroin solution at 0° and recrystallizing the crystallizate from methanol (36.6%), cooling the ligroin mother liquor in Dry Ice (3.9%), and concentrating the methanol mother liquor (3.2%). The material left undissolved by the ligroin consisted of crude hydroxynaphthoquinone amounting to a 21.6% recovery. Approximate solubilities observed for M-1916 are as follows: 1.5 g./100 cc. 95% alcohol at 30°, 6.6 g./100 cc. benzene at 20°, 0.4 g./100 cc. propanediol-1,2 at 30°; very soluble in tricaprylin, negligibly soluble in water.

M-1971 (K. E. H. and F. Minard).—Cyclohexylbutyric acid (935 g.) was refluxed with absolute ethanol (1.2 l.), toluene (0.9 l., more later) and 96% sulfuric acid (4 cc.) until water ceased to collect in a take-off, the solvent was removed and the ester distilled (yield 95.7%). Hydrogenolysis over copper chromite at 250°/3000 lb. (minimum) gave γ-cyclohexylbutanol,[1] $n^{28}D$ 1.4652; yield 90.5%. The bromide (b. p. 129° (19 mm.), $n^{25}D$ 1.4845) was prepared in 83.4% yield with phosphorus tribromide, and a mixture of 395 g. of bromide, 2.1 l. of alcohol, and a solution of 105 g. of sodium cyanide and 1.5 g. of potassium iodide in 420 cc. of water was refluxed with stirring for sixteen hours. A solution of 480 g. of potassium hydroxide in 300 cc. of water was added and the mixture refluxed thirty hours longer and then steam distilled. The solution was cooled, acidified, and the γ-cyclohexylvaleric acid[1] extracted with ether and distilled; b. p. 126–127° (0.5 mm.), m. p. 16.6–16.9°, yield 83.7%. A total of 3.12 moles of the acid chloride, employed in six alkylations, gave 275 g. of crude M-1971 and 200 g. (41%) of twice crystallized, satisfactory product, m. p. 107–108°. The yield of peroxide, by titration, was usually 90% or better.

M-297 (W. G. D.).—The required intermediate, a stereoisomeric mixture designated γ-2-"*trans*"-decalylbutyric acid was obtained most conveniently from γ-ar-2-tetralylbutyric acid (Paper VIII) by hydrogenation of the ester over nickel. A mixture of 156 g. of the acid, 345 cc. of methanol and 8 cc. of 96% sulfuric acid was refluxed for two hours, excess solvent was removed in vacuum, the ester was collected by ether extraction and distilled; the yield of methyl γ-ar-2-tetralyl butyrate, b. p. 136–138 (0.9 mm.), was 157 g. (95%). The ester was redistilled over Raney nickel (1 teaspoonful) and a 550-g. portion placed in a pressure bomb with 25–30 cc. of settled Raney nickel. The pressure initially should be 3500 lb./sq. in. at 30° and should be kept above 2000 lb. during the reaction conducted at 145°. Usually the reduction was complete in sixty to eighty hours. When absorption appears complete, a 10-cc. sample is removed, distilled, and the refractive index noted; a value of 1.4830 to 1.4840 at 25° is acceptable[2]; otherwise the ester is filtered through Celite to remove catalyst, fresh catalyst is added and the hydrogenation continued. The hydrogenated ester was warmed on the steam-bath with two equivalents of 10% sodium hydroxide and 25–50 cc. of methanol, when a mild exothermic reaction ensued; after being heated for fifteen minutes the solution was cooled, acidified and diluted and the oily layer collected with ether and distilled; b. p. 178–180° (1–1.5 mm.), $n^{25}D$ 1.4932; yield 90–95%.

Early attempts were made to force hydrogenation of the ester at 240°, but apparently some hydrogenolysis of the ester group occurred. Hydrogenation of the acid as sodium salt was tried with little success. The less accessible methyl γ-2-naphthylbutyrate (b. p. 185–188° (1.7 mm.)) was also tried as starting material but is now considered to offer no advantage, for a successful hydrogenation apparently proceeds through the same tetralyl intermediate. The success of the process described is dependent upon the use of highly pure ester and on the maintenance of a high pressure and a moderate temperature.

The acid chloride, prepared with thionyl chloride in 94–98% yield, boiled at 138–140° (1 mm.). Peroxide prepared by the hydrogen peroxide method at −3 to −8° was obtained in 75–85% yield (by titration). The alkylation mixture was worked up by the method (a) and the product crystallized from ligroin and then methanol. The average yield of satisfactory material based on titrated peroxide was 33.2%. Material supplied to the CMR Survey office was from a homogenized batch, m. p. 111–124°, made by mixing three batches of the following analyses.

Anal. Calcd. for $C_{23}H_{28}O_3$: C, 78.37; H, 8.00. Found: C, 78.37, 78.57, 78.55; H, 8.11, 7.90, 7.76.

The solubility in methanol is about 2 g./100 cc. at 25°.

M-2279 (A. G. W.).—For the preparation of γ-2-*cis*-

(1) Hiers and Adams, THIS JOURNAL 50, 1970 (1928).

(2) A solution of the fully reduced acid in 5% alkali when treated with a few drops of permanganate solution slowly turns blue and then green, whereas a solution of the tetralyl acid immediately turns to a dirty purple containing suspended manganese dioxide. The addition of dilute bromine solution to a solution of each acid in acetic acid produces a yellow to brown solution in the first case; in the second case the first few drops are almost completely decolorized.

decalylbutyric acid by hydrogenation of γ-ar-2-tetralylbutyric acid in acetic acid in the presence of Adams catalyst at a slight positive pressure it is essential to use acid that has been freshly distilled over Raney nickel. Batches that had been so processed but allowed to stand for several days gave unsatisfactory performance. The completeness of reduction in this case is best judged from the melting point of the product. In large-scale operation the product was distilled and then recrystallized from ligroin to a melting point of 81–84° (65% yield).[3] The acid chloride (thionyl chloride, 90% yield) boils at 145° (1 mm.). We are greatly indebted to the Lucidol Corporation, Buffalo, N. Y., for preparing the peroxide from about 4 kg. of acid and conducting the alkylation. The largest lot of peroxide used was 2.14 moles (from about 1 kg. of acid); extraction of the quinone (at Harvard) from the evaporated reaction mixture gave an average yield of 36% of M-2279 of the properties recorded in Table VIII. The reaction mixture was processed as in (a) and the ethereal solution washed first with bicarbonate to remove hydroxynaphthoquinone and then shaken with portions of 10% sodium carbonate to remove the bulk of the acid by-product until the red sodium salt of the quinone began to separate as an oil at the interface. The ether layer containing suspended red oil was acidified and shaken until the red salt was decomposed, and the solution was dried and the solvent displaced by 70–90° ligroin. The main crop separated on cooling, and more was obtained by shaking the mother liquor with 20% sodium hydroxide to precipitate red sodium salt. Final crystallization was done from methanol containing a few drops of hydrochloric acid.

Steric Forms of M-2279 (F. C. C.).—By careful fractional crystallization of M-2279 (m. p. 121–125.5°) from a not too concentrated methanol solution, two crystalline products were obtained of the melting points given in Table VIII: A, as dense, orange-yellow prisms; B as feathery, bright yellow needles. A mixture of the two melted at 126.5–128.5°. On one occasion a sample of the best prisms on repeated recrystallization gave rise to feathers in the mother liquor. Acetylation with acetic anhydride in pyridine gave acetates that seemed to be different: A, well shaped yellow needles, m. p. 100.5–102°; B, fine micro needles of a much lighter color, m. p. 92–93.5°.

Anal. Calcd. for $C_{25}H_{30}O_4$: C, 76.11; H, 7.67. Found: (A) C, 76.00, 75.90; H, 7.79, 7.30. (B) C, 76.42; H, 7.86.

Hydrolysis of the pure A acetate gave material that yielded both prisms, m. p. 128–129.5°, and feathers, m. p. 114–117°. Reductive acetylation of A and B gave colorless products melting, respectively, at 150–151° (from petroleum ether) and 130–133° (from methanol). Although some of these observations suggest polymorphism, it is perhaps more likely that A and B are not completely homogeneous stereoisomers.

A quinone apparently identical with the prism form A was synthesized from *cis*-β-decalone (76 g.) and methyl γ-bromocrotonate following the Reformatsky procedure of Ziegler.[4] The reaction product, b. p. 171–189° (1 mm.) (41% yield) was dehydrated with potassium bisulfate at 200° and the distillate, b. p. 152–165° (1.5 mm.), was hydrogenated. Hydrolysis and crystallization from petroleum ether gave material melting at 82–83° and showing no depression when mixed with the regular M-2279 acid intermediate. Peroxide alkylation with the synthetic acid gave quinone that crystallized in dense prisms, m. p. 125–127°, and did not depress the m. p. of isomer A.

Anal. Calcd. for $C_{23}H_{28}O_3$: C, 78.37; H, 8.00. Found: C, 78.37; H, 8.05.

This synthesis shows that M-2279 contains at least some material of the *cis*-decalyl configuration. Further work on the problem of isomerism was dropped when the assay results indicated that the prisms and feathers have substantially the same antimalarial activity.

By-products of Peroxide Alkylation[5] (C. H.) (a) **RCO_2H.**—An aliquot portion of the ligroin mother liquor remaining from the large-scale preparation of M-1916 was evaporated and a solution of the residue in ether extracted repeatedly with bicarbonate and then alkali. The combined acidic material when recovered and distilled yielded a slightly yellowish product corresponding closely in physical constants to pure γ-cyclohexylbutyric acid and affording pure M-1916 when used in a further alkylation. The recovery corresponded to 45% of the acid originally present in the form of the peroxide.

(b) **RR.**—An aliquot portion of the mother liquor corresponding to an original 1.08 moles of peroxide was washed free of naphthoquinone pigment with alkali and then extracted with 96% sulfuric acid (20 portions) until no further color was removed. The residual neutral material (5.0 g.) on distillation gave as the main fraction a product boiling at 143° (0.3 mm.) and identified as **1,6-dicyclohexylhexane** by comparison with a sample of the hydrocarbon (b. p. 155 (0.9 mm.)) synthesized by a known method.[6]

Anal. Product isolated: Calcd. for $C_{18}H_{34}$: C, 86.32; H, 13.68. Found: C, 86.61; H, 13.92. $n^{21}D$ 1.4758, d_{21} 0.8702, M_R 81.15 (calcd. 80.92). Product Synthesized: Found: C, 86.39; H, 14.00. $n^{21}D$ 1.4759, d_{21} 0.8702.

(c) **$ROCOCH_3$.**—An aliquot corresponding to an original 1.78 moles of peroxide was washed neutral with alkali and the collected product separated into the following fractions: 14.0 g., b. p. below 82° (0.5 mm.); 2 g. intermediate; 24.0 g. (0.1 mole) of 1,6-dicyclohexylhexane, b. p. 142–150° (0.5 mm.). The first fraction on distillation through a packed column at atmospheric pressure gave as the main fraction, b. p. 218–225°, a liquid of penetrating odor, soluble in 96% sulfuric acid, and corresponding in analysis to **γ-cyclohexylpropyl acetate**; $n^{21}D$ 1.4549, d_{20} 0.9395.

Anal. Calcd. for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94. Found: C, 71.39; H, 11.17.

Skita[7] records the constants: b. p. 120–121° (15 mm.), d_{20} 0.9398. Saponification of the ester gave **3-cyclohexylpropanol-1**, which after two distillations boiled at 63° (2 mm.); $n^{25}D$ 1.4601; d^{25} 0.937.

Anal. Calcd. for $C_9H_{18}O$: C, 76.00; H, 12.73. Found: C, 75.89; H, 12.64.

The **phenylurethan**, crystallized four times from petroleum ether, melted at 85–85.5°.

Anal. Calcd. for $C_{16}H_{23}O_2N$: C, 73.50; H, 8.87; N, 5.38. Found: C, 73.80; H, 8.64; N, 5.51.

An identical phenylurethan was obtained from the alcohol prepared by complete hydrogenation of cinnamaldehyde over Adams catalyst and a trace of ferrous sulfate.

(d) **RH.**—Since any cyclohexylpropane (b. p. 154°) formed in the preparation of M-1916 would have been removed in the course of the evaporation of acetic acid in vacuum, the neutral fraction recovered from the synthesis of 2-hydroxy-3-(γ-2′-decalylpropyl)-1,4-naphthoquinone (M-297) was examined for the presence of an RH by-product. After exhaustive washing of a ligroin solution with 96% sulfuric acid, distillation afforded a fraction of composition corresponding to 2-*n*-propyldecalin; b. p. 84° (4.3 mm.), d_{25} 0.8850, $n^{25}D$ 1.4734, $n^{20}D$ (calcd.) 1.4754.

Anal. Calcd. for $C_{13}H_{24}$: C, 86.58; H, 13.42. Found: C, 86.30; H, 13.37.

(3) A sample crystallized twice each from 30–60° and 60–90° ligroin melted at 85–86.2°. Calcd. for $C_{14}H_{24}O_3$: C, 74.95; H, 10.78. Found: C, 75.48; H, 11.21. The amide, after many recrystallizations, melted at 124–129.5°. Calcd. for $C_{14}H_{25}ON$: C, 75.28; H, 11.28. Found: C, 75.64; H, 11.26.

(4) Ziegler, Schumann and Winkelmann, *Ann.*, **551**, 120 (1942).

(5) By-products isolated in the preparation of quinones of other series are: RCO_2R and ROH (M-400, M-401, VI); RCO_3R (M-2282, VIII); RR (M-2334, VIII).

(6) Kuhn and Winterstein, *Ber.*, **60**, 433 (1927); *Helv. Chim. Acta*, **11**, 104 (1928).

(7) Skita, *Ber.*, **48**, 1692 (1915).

The constants are intermediate between those reported for the pure *cis* and *trans* isomers.[8]

(e) **Other Observations.**—A number of exploratory experiments were made on the decomposition of di-(cyclohexylbutyryl) peroxide in acetic acid in the presence and absence of hydroxynaphthoquinone, in ordinary and in purified acetic acid, etc., but the results justify no more than brief mention. When the peroxide was decomposed alone, the products (a), (b) and (c) were again isolated, and in addition the RH product was found present. Thus fractionation of the neutral material from 0.15 mole of peroxide through a Podbielniak column gave a first fraction of 8.25 g. (0.066 mole) of 1-cyclohexylpropane, b. p. 153–154°. When washed with 96% sulfuric acid and redistilled, the material had the following constants, in agreement with literature values: d_{25} 0.798, $n^{25}D$ 1.4361.

Anal. Calcd. for C_9H_{18}: C, 85.63; H, 14.37. Found: C, 85.76; H, 14.65.

In view of the work of Kharasch and Gladstone,[9] a search was made for the presence of succinic acid but none was found. Semiquantitative observations indicated that the hydrocarbons RR and RH are formed in smaller amounts when the quinone acceptor is present than when the peroxide is decomposed in acetic acid alone. The results in general suggest that the alkylation proceeds by a free radical mechanism but they do not constitute a proof of the point.

Quinone Derivatives

M-1916 Hydroquinone Trisulfate, Potassium Salt (H. H.).—The hydroquinone (7.75 g.), prepared by reduction with hydrosulfite and extraction with ether, was added to a mixture of 5.7 cc. of chlorosulfonic acid, 19 cc. of pyridine and 48 cc. of carbon tetrachloride, and the resulting viscous material was worked with a stirring rod and warmed for twenty minutes. The solvent was decanted and found to contain 0.5 g. (6%) of M-1916. The gum was dissolved in methanol and methyl alcoholic potassium hydroxide was added until the solution just turned pink, when it was filtered from inorganic salts and diluted with ether to a volume of about 2 l. The resulting tan precipitate was clarified with Darco in 200 cc. of methanol and reprecipitated with 700 cc. of dry ether; the yield of light tan powder was 12.6 g. (74%). The analytical sample was purified by several further precipitations and was completely colorless.

The salt dissolves readily in water to give a faintly orange solution that is neutral and shows brilliant blue fluorescence. The addition of barium chloride produces no change until the solution is warmed, when barium sulfate promptly precipitates. On standing at 25° for one day the aqueous solution becomes distinctly orange and slightly acidic.

M-1916 Sodium Salt (F. C. C.).—Five grams of M-1916 was triturated with 25 cc. of 1.25 *N* sodium hydroxide at 40° and 100 cc. of warm water was added and the lumps were broken up. The mixture was warmed on the steam-bath until the solid had dissolved and the solution filtered and allowed to cool. The salt separated in dark red needles, which were collected and washed with a few drops of chilled dilute ammonia solution and dried at 100°. The salt is extensively hydrolyzed by pure water; about 1 g. can be dissolved in 100 cc. of 1% sodium carbonate solution. The salt is very soluble in ethanol or acetone.

M-1971 Carbethoxymethyl Ether (C. H.).—A solution of 5 g. of M-1971 in 20 cc. of alcohol was treated in an evaporating dish with 3 g. of sodium hydroxide in 10 cc. of water and the solution was evaporated until the alcohol and most of the water was removed. The remaining water was decanted from the oily red sodium salt, which was dissolved in 50 cc. of acetonitrile and refluxed with 4 cc. of ethyl bromoacetate. The solution became yellow in about two and one-half hours, and the solvent was then removed in vacuum and the residual solid crystallized from methanol; yield 3.4 g., m. p. 78.5–79°. Attempts to obtain the free acid were unsuccessful.

Notes on Intermediates

M-2239.—Ruzicka and Boekenoogen[10] prepared cyclooctylacetic acid from cycloöctanone and ethyl bromoacetate by treating the crude Reformatsky product with phosphorus tribromide, followed by potassium hydroxide, and hydrogenating the resulting cycloöctenylacetic acid. Intermediates and derived substances that have been analyzed and characterized for the first time in the present work are listed in Table B.

M-2335.—6-Cyclopentylhexanoic acid,[11] b. p. 113–115° (0.6 mm.), $n^{20}D$ 1.4790, was prepared starting with 5-cyclopentylpentanoic acid; the methyl ester b. p. 126–128° (10 mm.) was reduced by the Bouveault-Blanc method in 61% yield to **5-cyclopentylpentanol-1**, b. p. 117–118 (8 mm.) (urethan, m. p. 78–79°).

Anal. Calcd. for $C_{10}H_{20}O$: C, 76.84; H, 12.90. Found: C, 76.25; H, 12.78.

The **bromide**, prepared with phosphorus tribromide in benzene, distilled at 110–112° (8 mm.) (69.5%) and was converted into the **nitrile**, 126–127° (8 mm.), in 86% yield. Hydrolysis with hydrochloric-acetic acid gave the required acid in 86% yield (crystalline below room temperature).

M-407, M-408.—Phenylcyclopentane, prepared in 67% yield from cyclopentene according to Corson and Ipatieff,[12] was acetylated by the procedure used by Mayes and Turner[13] for the preparation of *p*-cyclohexylacetophenone. *p*-Cyclopentylacetophenone was treated with sulfur and morpholine by the general method of Schwenk and Bloch[14]; the yield of crude morpholide, m. p. 95–98°, was 75%. Hydrolysis was accomplished with the acetic-sulfuric acid mixture employed by Newman[15]; yield of product m. p. 65–67°, 82%. Hydrogenation of methyl *p*-cyclopentylphenyl acetate did not proceed smoothly. Considerable cleavage of the ester group occurred and the only product isolated, and that in low yield, was the desired 4-cyclopentylcyclohexylacetic acid; none of the reduced methyl ester was isolated.

A solution of 133 g. of the aromatic ester in 100 cc. of methanol was refluxed for one hour with 15 g. of Raney nickel, filtered, combined with 75 cc. of methanol used for washing the nickel, treated with 25 g. of fresh catalyst and hydrogenated at 150° and 4000 lb. pressure. More catalyst had to be added after an interval, and finally a rise in pressure was noted and the reaction stopped. The viscous reaction product was clarified in benzene solution and then treated with cold alkali until no more acid was extracted. Acidification of the filtered extract gave colorless material that after two crystallizations from dilute methanol yielded 44 g. of 4-cyclopentylcyclohexylacetic acid suitable for alkylation. The analytically pure acid melted over a wide range and hence consisted of both geometrical isomers. Alkylation with 40 g. of this mixture gave 31 g. of residual solid after extraction of hydroxynaphthoquinone. This contained a considerable amount of starting acid, which was removed by vacuum distillation (6.9 g., b. p. 165–168° (1.5 mm.)). The residual mixture was fractionally crystallized with the use of pentane, Skellysolve B, methanol, ethanol, isopropanol and glacial acetic acid at various points in the process, for the separation proved very difficult. There was finally obtained 0.6 g. of pure M-408 (fluffy aggregates of fine

(8) Levina and Kulikov, *J. Gen. Chem., U. S. S. R.*, **10**, 1189 (1940) [*Chem. Abst.*, **35**, 2881 (1941)].

(9) Kharasch and Gladstone, THIS JOURNAL, **65**, 15 (1943); see however Kharasch, Jensen and Urry, *J. Org. Chem.*, **10**, 386 (1945); Kharasch, McBay and Urry, *ibid.*, **10**, 394, 401 (1945).

(10) Ruzicka and Boekenoogen, *Helv. Chim. Acta*, **14**, 1319 (1931).

(11) Yohe and Adams, THIS JOURNAL, **50**, 1503 (1928).

(12) Corson and Ipatieff, "Organic Syntheses," Coll. Vol. II, 1943, John Wiley and Sons, Inc., New York, N. Y., p. 151.

(13) Mayes and Turner, *J. Chem. Soc.*, 507 (1929).

(14) Schwenk and Bloch, THIS JOURNAL, **64**, 3051 (1942).

(15) Newman, *J. Org. Chem.*, **9**, 518 (1944).

yellow needles) that by analogy with the results reported in Paper VI probably is the *trans* isomer. A lower-melting fraction of 2.1 g. was analyzed and submitted for assay as M-407; this undoubtedly consists predominantly of the *cis* isomer but the homogeneity was not ascertained.

Fractional crystallization of the acid distillate (6.9 g.) from pentane and from Skellysolve B yielded one of the isomeric forms of 4-cyclopentylcyclohexylacetic acid (probably *trans*) as large, shiny, very thin plates, m. p. 130–131° (Table A).

Stereoisomeric Acid Mixtures.—Seven of the quinones of Tables VI–VIII, like M-2279 and M-297, were prepared from the total mixture of isomers resulting from the hydrogenation of a benzene, naphthalene, or tetralin acid or ester (Table C). Nickel hydrogenations were conducted with methyl ester distilled over nickel; platinum hydrogenations were conducted in acetic acid with free acid obtained by saponification of the nickel-purified ester. The completeness of hydrogenation can be judged satisfactorily from the refractive index.

Other Acids.—The following acids and their acid chlorides (Chl.) had the boiling or melting points and refractive indices (at T, ° C.) indicated: cyclohexylacetic[16]: b. p. 114–115° (3 mm.), Chl. b. p. 56–57° (2 mm.); cyclohexylpropionic,[16] 118–119° (2 mm.), Chl. b. p. 65–67° (1 mm.); α-methyl-γ-cyclohexylbutyric,[17] from $C_6H_5(CH_2)_2$-$CH(CO_2C_2H_5)_2$, b. p. 127–129° (0.5 mm.), 1.4613 (25°), Chl. b. p. 79–80° (0.4 mm.); ω-cyclohexylcaproic,[18] m. p. 32–33°; menthylacetic,[19] b. p. 128–130° (0.3 mm.), 1.4677 (20°), Chl. b. p. 155–156° (15 mm.); cyclohexylnonanoic,[17] by hydrogenation of the aromatic acid, m. p. 52.5–53.5°; cyclopentylacetic,[20] from the 2-keto acid, Chl. b. p. 79–80° (25 mm.), cyclopentylpropionic,[21] from 2-carbethoxycyclopentanone, b. p. 135–140° (15 mm.), Chl. 105–110° (28 mm.), naphthenic, b. p. 92.8–9.5° (1 mm.), Chl. b. p. 59.2–60.5° (4 mm.), dihydrochaulmoogric.[22]

(16) Adams and Marshall, THIS JOURNAL, **50**, 1970 (1928).
(17) Levene and Marker, *J. Biol. Chem.*, **110**, 311 (1935).

Summary

This paper reports the synthesis of 2-hydroxy-3-alkyl-1,4-naphthoquinones with side chains of the types —$(CH_2)_n$-cyclopentyl, —$(CH_2)_n$-cyclohexyl, —$(CH_2)_n$-cycloöctyl, —$(CH_2)_n$-decalyl. Some evidence of the mechanism of the peroxide alkylation reaction is afforded by the isolation of a number of by-products.

(18) Hiers and Adams, THIS JOURNAL, **48**, 2385 (1926).
(19) Wallach and Schellack, *Ann.*, **353**, 317 (1907).
(20) Linstead and Meade, *J. Chem. Soc.*, 940 (1934).
(21) King, *ibid.*, 982 (1935).
(22) Sbriner and Adams, THIS JOURNAL, **47**, 2727 (1925).

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Naphthoquinone Antimalarials. IV–XI. Synthesis.

VI. 4′-Cyclohexylcyclohexyl and Cycloalkyl Series (and M-395, M-396)

The naphthoquinones listed in Tables IX and X, including the structurally related M-395 and M-396 transposed from Table XIII, are best considered from two points of view, as indicated in the following headings.

Stereoisomerism of 4′-Cyclohexylcyclohexyl Derivatives.—The most potent suppressants of avian malarial infections encountered in this work are 2-hydroxy-1,4-naphthoquinones with a 3-alkyl substituent containing the 4′-cyclohexylcyclohexyl group, which can exist in both the *cis* and *trans* configuration. From the starting materials indicated in the chart four pairs of stereoisomeric quinones were prepared in which the bicyclic group is separated from the naphthoquinone nucleus by three, two or one methylene group, or is directly joined to the nucleus. Two other pairs of isomers synthesized by peroxide alkylation have as 3-substituents the 4′-phenylcyclohexylmethyl and the 4′-phenylcyclohexyl groups. In four instances where both the *cis* and *trans* acids were isolated in a pure form the carboxyl group was separated from the ring system by one or more methylene groups, and all alkylation experiments with sterically pure acids of this type indicated that a single, sterically pure quinone is produced and that the higher melting of two isomeric acids affords a quinone that melts higher than its geometrical isomer. Evidently no steric change occurs in alkylations with peroxides in which the carboxyl carbon is separated from the ring system by at least one methylene group. When the carboxyl group is attached directly to the ring (acids IX, X) the original configuration is not retained and alkylation with the peroxide of either a sterically pure acid or an isomer mixture gives a mixture of the *cis* and *trans* substituted quinones; in each case the mixture was separated and the two components isolated. The preparative experiments thus made available four pairs of isomeric acids and six pairs of isomeric quinones, the components of four of which were known to have the same configurations as the acid precursors.

Further interrelationships were established as follows. Among the acids of melting points higher than their isomers it was possible to correlate the pairs II and IV, and VI and IX by Wieland–Barbier degradation. By hydrogenation of the benzene ring, a correlation was established between acids VIII and VI and between X and IX. Confirmatory correlations were accomplished in the series of lower melting acids between I and III and between V and VII. These observations confirm the configurational relationship established by Nenitzescu and Gavat[1a] by Wieland–Barbier degradation of VIII to X. Since the completion of this work Posvic[1b] has reported the preparation of the acids V, VI and IX by methods different from those employed here; our conclusions regarding the configurational relationships agree

(1a) Nenitzescu and Gavat, *Ber.*, **70**, 1883 (1937).
(1b) Posvic, paper presented at the Chicago meeting of the American Chemical Society, September, 1946.

TABLES IX AND X

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

PA = Peroxide alkylation. HO = Hooker oxidation. D = Diene synthesis. S = Sodium hydroxide method. H = Hydrogen peroxide method. i = Peroxide isolated. t = Peroxide titrated.

M-	3-Alkyl side chain (-C_6H_{10}·C_6H_{11} = 4′-cyclohexylcyclohexyl-)	Formula	M. p., °C.	Prepared by	Method	Perox. Yield, %	RCOC Quinone yield, %	$(RCOO)_2$	Solvent for cryst.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
	IX. 4′-CYCLOHEXYLCYCLOHEXYLALKYL SERIES												
384	-CH_2-C_6H_{10}·C_6H_{11}-*cis*	$C_{23}H_{38}O_2$	129–130	H. E. Z.	PA		See text		Pet. ether	78.37	78.38	8.00	8.32
		$C_{23}H_{38}O_2$	Identical	M. F.	HO		29		EtOH	78.37	78.40	8.00	8.38
380	-CH_2-C_6H_{10}·C_6H_{11}-*trans*	$C_{23}H_{38}O_2$	209–210	H. E. Z.	PA		30[a]		EtOH	78.37	78.58	8.00	7.93
2329	-CH_2CH_2-C_6H_{10}·C_6H_{11}-*cis*	$C_{24}H_{40}O_2$	151–152	M. F.	PA	H39t	29[a]		EtOH	78.65	78.72	8.25	8.58
		$C_{24}H_{40}O_2$	Identical	M. F.	HO		23		MeOH	78.65	78.75	8.25	8.58
2330	-CH_2CH_2-C_6H_{10}·C_6H_{11}-*trans*	$C_{24}H_{40}O_2$	164.5–165[b]	M. F.	PA	H36t	36[a]		EtOH	78.65	78.84	8.25	8.39
2291	-$CH_2CH_2CH_2$-C_6H_{10}·C_6H_{11}-*cis*	$C_{25}H_{42}O_2$	111–112	M. F.	PA	H81t	25[a]		Lig., MeOH	78.91	79.20	8.48	8.44
2292	-$CH_2CH_2CH_2$-C_6H_{10}·C_6H_{11}-*trans*	$C_{25}H_{42}O_2$	180–180.5	M. F.	PA	H97t	31[a]		C_6H_6-Lig.	78.91	79.24	8.48	8.43
	X. CYCLOALKYL SERIES												
2326	-Cyclopentyl	$C_{15}H_{14}O_2$	99–100[c]	E. W.	HO		(64)		Dil. MeOH	74.35	74.65	5.82	6.14
266	-Cyclohexyl	$C_{16}H_{16}O_2$	136.5–137.5	K. E. H.	PA	S	17		Pet. ether	74.98	75.17	6.29	6.37
			136.5–137.5	W. G. D.	PA	S	16		Aq. MeOH	74.98	74.92	6.29	6.52
2328	-β-Decalyl-*cis* (mixt.)	$C_{20}H_{32}O_2$	161.5–163	C. H.	PA	H80t	1.9		MeOH	77.39	77.60	7.15	7.48
2374	-β-Decalyl-*trans*	$C_{20}H_{32}O_2$	121–122	C. H.	D				Aq. HOAc	77.39	77.37	7.15	7.41
411	-C_6H_{10}-4′-cyclopentyl (mixt.)	$C_{21}H_{34}O_2$	130–139	H. E. Z.	HO				Pentane	77.75	77.84	7.46	7.30
412	-C_6H_{10}-4′-cyclopentyl	$C_{21}H_{34}O_2$	179–180.5	H. E. Z.	HO				Pentane	77.75	77.87	7.46	7.38
2327	-C_6H_{10}·C_6H_{11}-*cis*	$C_{22}H_{36}O_2$	166–166.5[d]	M. F.	PA	H	See text		MeOH	78.07	77.82	7.74	7.65
			Identical	M. F.	HO		13						
2293	-C_6H_{10}·C_6H_{11}-*trans*	$C_{22}H_{36}O_2$	195.5–196.5	M. F.	PA	H	See text		EtOH	78.07	77.83	7.74	7.93
			Identical	M. F.	HO		5						
401	-Cyclohexyl-4′-C_6H_5-*cis*	$C_{22}H_{30}O_2$	136–137	H. E. Z.	PA	S	1.7[e]			79.50	79.66	6.07	6.04
			Identical	H. E. Z.	HO								
400	-Cyclohexyl-4′-C_6H_5-*trans*	$C_{22}H_{30}O_2$	212–213	H. E. Z.	PA	S	1.5[e]			79.50	79.62	6.07	6.05
396	-CH_2-Cyclohexyl-4′-C_6H_5-*cis*	$C_{23}H_{32}O_2$	140.5–141.5	H. E. Z.	PA	S	25[e]		MeOH	79.74	80.05	6.40	6.32
395	-CH_2-Cyclohexyl-4′-C_6H_5-*trans*	$C_{23}H_{32}O_2$	174–175	H. E. Z.	PA	S	7.7		EtOH	79.74	79.81	6.40	6.21

[a] Yield from sterically pure acid. [b] Purified through the acetate m. p. 95.5–96.5° (Calcd.: C, 76.50; H, 7.89. Found: C 76.32; H, 7.60). [c] Paper XII. [d] Purified through the acetate, m. p. 142–143° (Calcd.: C, 75.78; H, 7.42. Found: C, 76.02; H, 7.66.

with his. That the two sets of six quinones each, listed by code numbers at the extreme right and left sides of the chart, belong to two steric series was established by the conversion of several of the compounds into their lower homologs by Hooker oxidation, which proceeds with complete retention of configuration. The correlation established in this way between quinones of both the higher melting and lower melting series, coupled with the fact that alkylations with acids II, IV and VI and their isomers proceed with retention of configuration, provides a correlation, not established directly, between the acids II and IV and the acids of the directly related group VI, VIII, IX and X.

The problem of establishing the absolute configurations of the two series of quinones and acids was solved by the ozonization of the higher melting of the two known 4′-phenylcyclohexanecarboxylic acids, X. The reaction was conducted under conditions precluding an isomerization[1c] and gave the high-melting hexahydroterephthalic acid of rigorously established *trans* configuration,[2] XI. Therefore, the six quinones at the right of the chart, and the corresponding six acids, all have the *trans* configuration. The higher melting 4-phenylcyclohexylacetic acid thus is the *trans* isomer, whereas the higher melting 2-phenylcyclohexylacetic acid has been shown to have the *cis* configuration.[3] Of the two isomeric forms of 4′-cyclohexylcyclohexanol-1, the higher melting one has been assigned the *cis* configuration.[4]

In the series of quinones with the substituent $-(CH_2)_n$-4′-cyclohexylcyclohexyl-*cis*, where n = 0, 1, 2 and 3, the melting points are: 166.5, 130, 152 and 112°; in the corresponding *trans* series the values are: 196.5, 210, 165 and 180.5°. Although the data are limited, it may be significant that alternation occurs in each series and that the high melting homologs of the *cis* and *trans* series are those having, respectively, an even and an odd number of carbon atoms in the side chain.

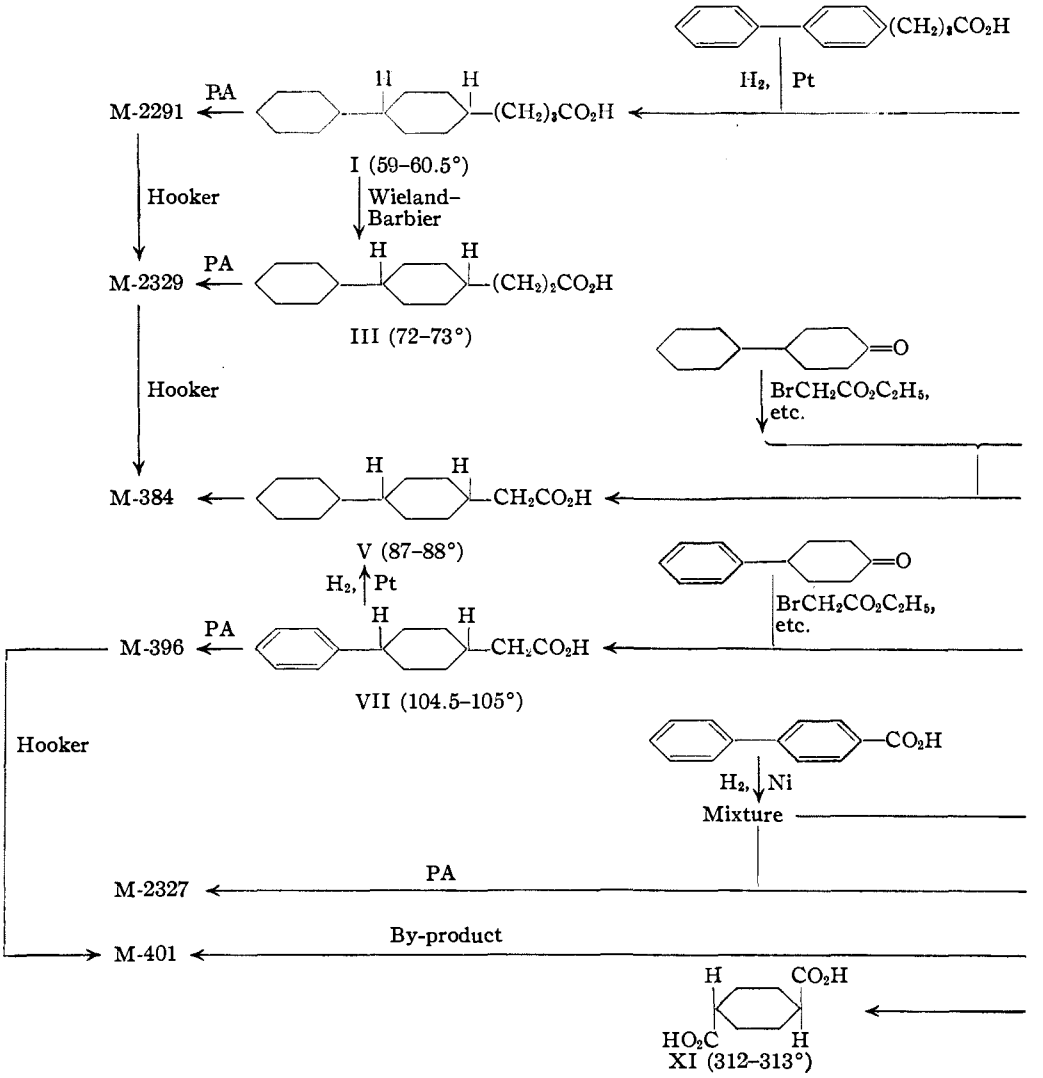
Synthesis of Compounds Having a Cycloalkyl Group Attached Directly to the Quinone Ring.—Compounds of the type defined are endowed with greatly enhanced potency but, unfortunately, are particularly difficult to synthesize by methods that afford an easy route to the methyl-

(1c) Rassow, *Ann.*, **282**, 139 (1894).

(2) Mills and Keats, *J. Chem. Soc.*, 1373 (1935).

(3) Linstead, Whetstone and Levine, THIS JOURNAL, **64**, 2014 (1942).

(4) Schrauth and Görig, *Ber.*, **56**, 1900 (1923).



ene homologs. Six cycloalkyl-substituted quinones listed in Table X were obtained by peroxide alkylation, but the yield usually was in the order of 1–2% and in the best case (M-266) was only 16–17%. At a time when M-2293 appeared, because of its remarkably high potency in the duck assays, to be the most promising of all the naphthoquinones, considerable effort was made to find an alternate method for the synthesis of this and related cycloalkyl derivatives. Some progress was made in the adaptation of the diene synthesis (Paper III; synthesis of M-2374), but none of several methods explored for the direct hydrocarbon alkylation of a benzo- or naphtho-quinone or hydroquinone, or for a ring-closure synthesis, could be developed into a satisfactory process. The Experimental Part includes a brief record of the few positive results that had accumulated at the time the work was dropped because of the recognition that M-2293 is deficient with respect to resistance to metabolic degradation.

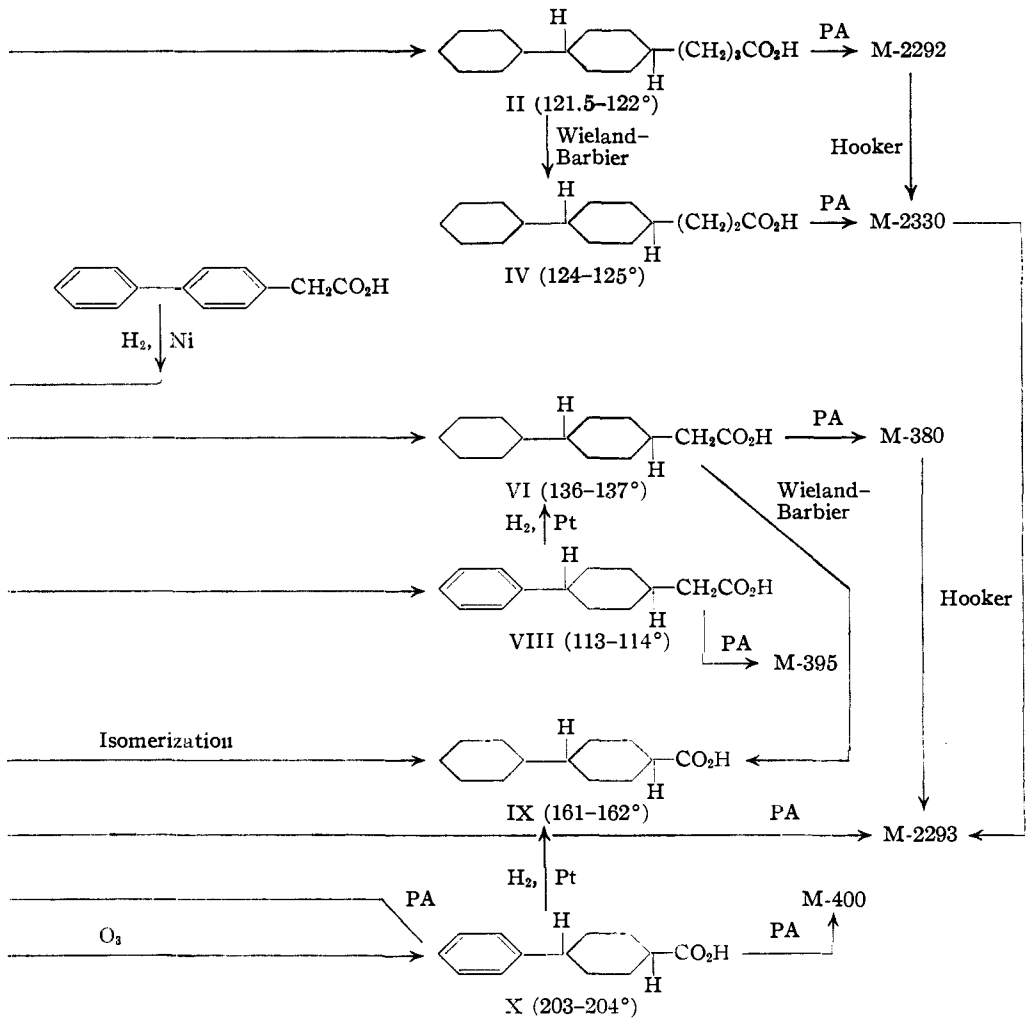
Experimental

4′-Cyclohexyl(and 4′-Phenyl)-cyclohexyl Derivatives

Intermediates.—The following paragraphs describe the methods used for the preparation of the acid intermediates, listed by pairs in the order in which they appear in the chart. The properties and analyses of these and other intermediates and derivatives are recorded in Table A.

Acids I and II.—Hydrogenation of γ-*p*-xenylbutyric acid as ester over Raney nickel and hydrolysis gave an acid mixture that in the alkylation reaction afforded only one of the quinones (M-2292), and that in low yield. The hydrogenation of the free acid over Adams catalyst gave material from which the pure *cis* and *trans* acids could be separated by fractional crystallization from petroleum ether (*trans* less soluble). In a later experiment (F.C.C.) the starting material was purified by Soxhlet extraction with 30–60° ligroin; hydrogenation then proceeded very rapidly (twenty hours for 22 g.) and when the filtered acetic acid solution was diluted and allowed to crystallize slowly the *cis* isomer separated first and was obtained pure by one recrystallization in 62% yield.

Acids III and IV.—The methyl ester of II (22 g.) was treated with the Grignard reagent from 32.5 g. of bromobenzene in the usual way and the semicrystalline diphenylcarbinol refluxed for four hours with 150 cc. of acetic an-



hydride and 100 cc. of acetic acid. The residue left on removal of the solvent in vacuum was crystallized from petroleum ether (Table A). Chromic acid oxidation of the diphenylethylene by a standardized procedure[5] afforded acid IV in only 45% yield and the result was not improved by employing a special procedure of Kendall.[6] The *cis* acid III was prepared in exactly the same way.

Acids V and VI.—The first synthesis was from commercial 4-cyclohexylcyclohexanol, which was oxidized to 4-cyclohexylcyclohexanone,[4] b. p. 104–110° (1 mm.), in 63% yield by a procedure described for the 2-isomer.[7] A Reformatsky reaction was carried out as described for the isomer[7] and the hydroxy ester was not isolated but was dehydrated in the prescribed manner (see Table A). Saponification of the saturated ester gave a solid acid with a wide melting range. Repeated crystallization from Skellysolve B gave colorless plates of VI, and careful and tedious fractional crystallization from pentane of the more soluble residues gave a small amount of V in the form of colorless flat needles. The second method was by hydrogenation of methyl *p*-xenylacetate. The ester derived from acid prepared by the Willgerodt reaction was freed of sulfur by refluxing a solution of 226 g. of ester in methanol with 15 g. of Raney nickel for one hour and then filtering. Fresh nickel (25 g.) was added and hydrogenation conducted at 150° (4000–5000 lb./sq. in.); the reaction stopped after a time and the solution was filtered and fresh catalyst added. From 525 g. of acid mixture resulting on hydrolysis there was obtained in four recrystallizations, each time from four volumes of Skellysolve B, a total of 108 g. of VI, m. p. 136–137° (no depression in mixed m. p.). The residual material from the mother liquor was recovered and used in alkylations.

Acids VII and VIII.—Crude 4-phenylcyclohexanol[8] was oxidized in the usual manner[7] and the 4-phenylcyclohexanone purified through the bisulfite compound[9]; the yield from 265 g. of alcohol was 109 g. (42%) of ketone, obtained from Skellysolve B as heavy needles, m. p. 76–77°, having a pleasant rose-like odor. A Reformatsky reaction and dehydration without isolation of the carbinol gave ethyl 4-phenyl-Δ^1-cyclohexenylacetate. Hydrogenation was conducted in ethanol in the presence of Adams catalyst, and the temperature was kept from rising above 50°. Saponification of the saturated ester and distillation afforded a solid isomer mixture. This material (105 g.) was finely ground and refluxed for three hours with 2.5 l.

(5) Riegel, Moffet and McIntosh, "Organic Syntheses," **24**, 38 (1944).

(6) Private communication from Dr. E. C. Kendall.

(7) Cook, Hewett and Lawrence, *J. Chem. Soc.*, 71 (1936).

(8) Musser and Adkins, THIS JOURNAL, **60**, 664 (1938).

(9) von Braun and Weissbach, *Ber.*, **64**, 1788 (1931).

TABLE A

STEREOISOMERIC ACIDS AND INTERMEDIATES

Compound (C_6H_{11}·C_6H_{10}- = 4-cyclobexylcyclobexyl-)	Formula	Method	Yield, %	M. p. or b. p., °C.	Mm.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
Methyl γ-*p*-xenylbutyrate				b 212–215	3				
C_6H_{11}·$C_6H_{10}(CH_2)_2CO_2CH_3$ (mixt.)		Ni-hydr. est. 145°	83	b 153–156	1.1				
C_6H_{11}·$C_6H_{10}(CH_2)_2CO_2H$ (I + II)		Hydrol.		b 198	1.7				
Chloride (→ M-2292)		$SOCl_2$ in C_6H_6	84	b 166–168	2				
C_6H_{11}·$C_6H_{10}(CH_2)_2CO_2H$-*trans* (II)	$C_{15}H_{28}O_2$	Pt-hydr. HOAc	18	m 121.5–122		76.14	76.23	11.18	11.23
Chloride		$SOCl_2$	84	b 169–172	2.5				
Methyl ester	$C_{17}H_{30}O_2$	RCOCl + CH_3OH		b 157	1.3[a]	76.64	76.78	11.35	11.07
Amide	$C_{15}H_{29}ON$			m 187.5–189		76.41	76.56	11.63	11.27
C_6H_{11}·$C_6H_{10}(CH_2)_2CO_2H$-*cis* (I)	$C_{15}H_{28}O_2$	M. L. of II	22–62	m 59–60.5		76.14	76.45	11.18	11.41
Chloride		$SOCl_2$	81	b 177–178	1.9				
Methyl ester	$C_{17}H_{30}O_2$	RCOCl + CH_3OH		b 144	0.5[b]	76.64	77.01	11.35	11.57
Amide	$C_{15}H_{29}ON$					76.41	76.35	11.63	11.29
C_6H_{11}·$C_6H_{10}(CH_2)_2CH{=}C(C_6H_5)_2$-*trans*	$C_{28}H_{36}$	Grig.; dehydrat.	72	m 80–80.5		90.26	90.66	9.74	9.83
C_6H_{11}·$C_6H_{10}(CH_2)_2CO_2H$-*trans* (1V)	$C_{16}H_{28}O_2$	CrO_3, cryst. P. E.	45	m 124–125		75.58	75.60	11.00	11.04
Chloride		$SOCl_2$	84	b 144–146	0.7				
Amide	$C_{16}H_{27}ON$			m 177.5–178.5		75.86	76.05	11.47	11.16
C_6H_{11}·$C_6H_{10}(CH_2)_2CH{=}C(C_6H_5)_2$-*cis*	$C_{28}H_{36}$	As above	74	b 230–237	1	90.26	89.66	9.74	9.79
C_6H_{11}·$C_6H_{10}(CH_2)_2CO_2H$-*cis* (III)	$C_{16}H_{28}O_2$	As above	41	m 73–74		75.58	75.93	11.00	10.98
Chloride				b 142–145	0.7				
Amide	$C_{16}H_{27}ON$			m 120–121		75.86	75.67	11.47	11.31
Et 4-cyclobexyl-Δ^1-cyclohexenylacetate	$C_{16}H_{28}O_2$	Reformatsky	52	b 131–134	0.5[c]	76.75	77.05	10.46	9.87
C_6H_{11}·$C_6H_{10}CH_2CO_2C_2H_5$ (mixt.)		Ni-hydr. ester	75	b 106–109	0.1[d]	76.11	76.39	11.22	11.14
Methyl *p*-xenylacetate		From acid	85	b 140–143	0.5[e]				
C_6H_{11}·$C_6H_{10}CH_2CO_2CH_3$ (mixt.)		Ni-hydr. ester	80	b 105–112	0.5[f]				
C_6H_{11}·$C_6H_{10}CH_2CO_2H$, Mixture A		Sapon. Ref. est.	90						
Mixture B		Sapon. hydrog. est.	98						
C_6H_{11}·$C_6H_{10}CH_2CO_2H$-*trans* (VI)	$C_{14}H_{24}O_2$	A or B fr. Sk. B.	21 (B)	m 136–137.5		74.95	74.96	10.78	10.86
C_6H_{11}·$C_6H_{10}CH_2CO_2H$-*cis* (V)	$C_{14}H_{24}O_2$	From M. L. of A		m 86.5–87.5		74.95	75.07	10.78	10.75
Ethyl 4-phenyl-Δ^1-cyclohexenylacetate		Reformat.	62	b 143–146	0.4[g]				
4-Phenyl-Δ^1-cyclohexenylacetic acid	$C_{14}H_{16}O_2$	Saponif. of ester		m 105–108		77.75	78.17	7.46	7.65
4-Phenylcyclohexylacetic acid (mixt.)		Pt-hydr. ester	92	m 70–85					
4-Phenylcyclohexylacetic acid-*cis* (VII)	$C_{14}H_{18}O_2$	Residue of extrn.	14	m 104.5–105		77.03	77.42	8.31	8.10
Amide	$C_{14}H_{19}ON$			m 168.5–169.5		77.38	77.56	8.81	8.62
4-Phenylcyclohexylacetic acid-*trans* (VIII)		From mother liquor		m 113–114					
Ethyl diphenyl-4-carboxylate		Ref. 15 (m. p. 49–53°)	93	b 165–170	2				
C_6H_{11}·$C_6H_{10}CO_2C_2H_5$ (mixt.)		Ni-hydrog. ester	87	b 120–122	0.5				
C_6H_{11}·$C_6H_{10}CO_2H$ (Ni-mixt.)		Saponif., cryst. P. E.		m 76–92					
Chloride		$SOCl_2$	91	b 122–126	0.9				
C_6H_{11}·$C_6H_{10}CO_2H$ (Pt-mixt.)		Pt-hydrog. of acid	91	m 85–95					
Chloride		$SOCl_2$	88	b 125.5–129	1				
Methyl ester of VI			94	b 127.5–128.5	0.4				
C_6H_{11}·$C_6H_{10}CH{=}C(C_6H_5)_2$	$C_{26}H_{32}$	Grig. on VI ester	77	m 82–83		90.64	90.50	9.36	9.49
C_6H_{11}·$C_6H_{10}CO_2H$-*trans* (IX)	$C_{11}H_{22}O_2$	(a) Isomeriz.	39	m 161–162		74.21	74.40	10.53	10.64
		(b) Oxidn.	49	m 161–162					
Chloride		$SOCl_2$	92	b 121	0.5				
Amide	$C_{12}H_{21}ON$	Plates from MeOH		m 202.5–203.5		74.60	74.61	11.06	10.69

$n^{25}D$: *a* 1.4785, *b* 1.4795, *c* 1.4930, *d* 1.4811, *e* 1.5890, *f* 1.4828, *g* 1.5263.

of pentane, and the undissolved portion was re-ground and digested for an hour with 1.5 l. of boiling pentane. The residual white powder (20 g., m. p. 95–102°) on several recrystallizations from Skellysolve B gave 15 g. of satisfactory *cis*-acid VII, and a sample recrystallized three times from methanol formed heavy needles, m. p. 104.5–105°. Hydrogenation of this acid in ethanol in the presence of platinum oxide gave a product, m. p. 87–88°, that did not depress the m. p. of acid V.

The pentane filtrates were combined (4 l.) and the recovered acid submitted to careful fractional crystallization. The more soluble fractions finally afforded a small amount of the *trans* acid VIII in the form of colorless needles, m. p. 113–114°. This did not depress the m. p. of an authentic sample prepared according to Nenitzescu and Gavat[10]; the amide melted at 194–195.5° (195° given). This isomer on hydrogenation as before gave a substance (m. p. 136–137°) identical with acid VI.

Acid IX.—The starting material, 4-acetodiphenyl, was prepared most satisfactorily on a large scale by Friedel and Crafts reaction in carbon bisulfide solution[11]; when benzene[12] was used appreciable amounts of acetophenone had to be separated, tar-formation occurred, and the yield of satisfactory product, m. p. 122–123°, was only 31% in a 500-g. run. Hypochlorite oxidation to diphenyl-4-carboxylic acid was conducted, more successfully than previously reported,[13] as follows. To the hypochlorite solution prepared by a standard method[14] from 820 g. of sodium hydroxide, 300 g. of finely powdered 4-acetodiphenyl was added, together with 1 g. of the detergent Naccanol. The mixture was stirred vigorously with a double Hershberg stirrer under an efficient reflux and heated continuously until an easily-read thermometer registered a temperature of 85–90°, when a vigorous exothermic reaction set in calling for efficient ice cooling.

(10) Nenitzescu and Gavat, *Ber.*, **70**, 1883 (1937).

(11) von Auwers and Julicher, *ibid.*, **55**, 2167 (1922); Long and Henze, THIS JOURNAL, **63**, 1939 (1941).

(12) Grieve and Hey, *J. Chem. Soc.*, 970 (1933).

(13) Gull and Turner, *J. Chem. Soc.*, 498 (1929).

(14) Newman and Holmes, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 428.

The reaction subsided after about two hours and the mixture was then refluxed gently for six hours longer. The reaction product separated as the sodium salt, which was collected after cooling and dissolved in 6 l. of boiling water. The filtered solution was acidified and the acid collected and dried to constant weight; yield (typical of several runs) 289 g. (95.5%), m. p. 224–226°. The precipitated acid is satisfactory for conversion to the ester for hydrogenation over nickel but should be crystallized at least once from alcohol prior to hydrogenation over platinum.

As indicated in Table A, batches of 4-cyclohexylcyclohexanecarboxylic acid were prepared by hydrogenation of the aromatic acid over platinum catalyst and of an ester over Raney nickel (the lower melting ethyl ester is more conveniently manipulated than the methyl ester[15] and is prepared by direct distillation of the esterification mixture—washed with water but not with bicarbonate—and redistillation over Raney nickel). It was not found possible to isolate pure isomer from either acid mixture until it has been submitted to a process of isomerization. Thus 90 g. of the nickel-hydrogenated ethyl ester was run slowly into 2.5 l. of absolute alcohol in which 100 g. of sodium had been dissolved and the solution was refluxed for seven days. Hydrolysis was accomplished by adding 100 cc. of water and refluxing for two days; the recovered acid on repeated crystallization from petroleum ether afforded 29.5 g. of pure *trans* acid IX, m. p. 161–162°. An identical acid (0.2 g.) was isolated after 2 g. of the isomer mixture had been heated for sixty hours in a sealed tube with 5 cc. of 36% hydrochloric acid. The same *trans* acid (mixed m. p.) was also obtained by degradation of acid VI, through the diphenylethylene listed in Table A and by hydrogenation of 4-phenylcyclohexanecarboxylic acid[16] (m. p. 203–204°) over Adams catalyst in acetic solution.

Ranedo and Leon[17] report the isolation of two supposed isomers, m. p. 76–78° and 105°, resulting from the platinum-hydrogenation of 4-diphenylcarboxylic acid, but the first yielded two amides, m. p. 164° and 197°, and the second gave the 197° amide. Since our *trans* amide melts at 203°, it is probable that both crystallizates were mixtures.

Proof of Configuration (M. G. E.).—The oxidation procedure was modeled on that of Linstead, Davis and Whetstone.[3] A solution of 1 g. of 4-phenylcyclohexanecarboxylic acid (X, m. p. 205–208°, cor.) in 35 cc. of acetic acid was treated with a rapid stream of ozone for three hours and the solution was then diluted with 50 cc. of 2% hydrogen peroxide, heated for one-half hour on the steam-bath and cooled in ice. A crystallizate of 0.4 g. of starting material was removed and the filtrate evaporated in vacuum and the product dissolved in 20 cc. of 5% sodium carbonate. The ether-washed solution was heated on the steam-bath, acidified and filtered hot to separate 40 mg. more of starting material, and then concentrated and cooled. The product that separated was recrystallized from 15 cc. of water and afforded 0.11 g. of *trans*-hexahydroterephthalic acid (XI), m. p. 312–313°, cor. (sealed tube, lit.[2] 309°).

Anal. Calcd. for $C_8H_{12}O_4$: C, 55.80; H, 7.03. Found: C, 55.60; H, 7.20.

The dimethyl ester, prepared with diazomethane, melted at 67.5–68.5° (lit.[18] 71°). The melting points reported for the *cis* acid and its dimethyl ester are 167°[2] and 3–5°.[19] In another experiment 2.4 g. of X, ozonized in three portions, yielded 0.42 g. (21%) of recrystallized XI.

Alkylations.—The yields of quinones obtained as the main products of alkylations utilizing sterically pure acids are given in Tables IX and X. Other alkylations were conducted with *cis-trans* mixtures, and sometimes both isomeric quinones were isolated. For example, M-384 (*cis*) was obtained in this way in 2.2% yield along with 0.6% of the pure *trans* isomer, M-380, and 7.8% of a mixture of the two quinones. In other instances, the peroxide derived from a sterically pure acid gave both *cis* and *trans* quinones. That no isomerization occurs in the formation of the acid chloride and peroxide was indicated by the reduction with potassium iodide of a *cis*-rich mixture from 4-cyclohexylcyclohexanecarboxylic acid (m. p. 85–93°); the product recovered had the same melting point characteristics as the starting acid. The alkylation of hydroxynaphthoquinone with the peroxide from pure *trans*-4-phenylcyclohexanecarboxylic acid gave a complex mixture from which, by tedious fractionation from Skellysolve B, Skellysolve C, methanol, ethanol and acetic acid the following products were isolated (in addition to a considerable amount of starting acid): M-400 (*trans*); M-401 (*cis*); 4-phenylcyclohexanol (m. p. 119–120°; identified by mixed m. p.); and a fourth product in the form of small colorless leaflets, m. p. 145–146°, identified as the **4-phenylcyclohexyl ester of 4-phenylcyclohexanecarboxylic acid** by synthesis as follows. A mixture of 2.43 g. of *trans*-4-phenylcyclohexanecarboxylic acid chloride[1] (colorless needles from pentane, m. p. 68–70°) and 1.93 g. of 4-phenylcyclohexanol (m. p. 118–120°) in 25 cc. of pyridine was heated on the steam-bath overnight. A crystalline deposit formed on cooling. The mixture was distributed between ether and water and the ethereal solution was washed with hydrochloric acid and with soda, dried and evaporated. The residual solid melted at 143–147° (2.5 g.); two crystallizations from alcohol gave small colorless leaflets, m. p. 146–147°.

Anal. Calcd. for $C_{25}H_{30}O_2$: C, 82.83; H, 8.34. Found: C, 83.16; H, 8.32.

This ester (*trans-cis* or *trans-trans*) did not depress the m. p. of the above by-product.

Decomposition of the Peroxide of 4-Phenylcyclohexanecarboxylic Acid (H. E. Z.) (a) In Acetic Acid.—A solution of 3.6 g. of the peroxide (shiny white leaflets from ether, m. p. 124–126°, dec.) in 50 cc. of acetic acid was heated for one and one-half hours at 95–100° and the hot solution poured into ice and water and worked up in the usual way. There was obtained 2.88 g. of crude material from which 1.55 g. of 4-phenylcyclohexanecarboxylic acid (m. p. 199–202°) and 0.15 g. of 4-phenylcyclohexanol (m. p. 115–117°) was isolated. None of the ester m. p. 146° could be obtained in pure form.

(b) **In Carbon Tetrachloride.**—A solution of 3.2 g. (0.00788 mole) of the peroxide in carbon tetrachloride was refluxed for two hours and the effluent carbon dioxide swept into 5% barium hydroxide with a stream of nitrogen; the precipitated barium carbonate when dried weighed 1.53 g. (0.00774 mole). The carbon tetrachloride was evaporated and the residue taken up in ether and washed with sodium carbonate solution, but no trace of starting acid was found present. The neutral material recovered from the ether melted over a wide range; several crystallizations from alcohol gave 1.0 g. of 4-phenylcyclohexyl 4'-phenylcyclohexylcarboxylate, m. p. 144–146°, identical (mixed m. p.) with the synthetic ester. A second crop of crystals, m. p. 134–140°, was found on analysis to have the same composition as this ester and hence probably contains one or more isomeric esters resulting from loss of configuration of the alcohol and (or) acid component during the peroxide decomposition. Attempts to isolate 4-phenylcyclohexanol were unsuccessful. The absence of both the alcohol and acid components in the product of decomposition in carbon tetrachloride suggests that the formation of these substances in the reaction in acetic acid in the absence of a quinone acceptor may be due to solvolysis of the initially formed ester.[20]

M-2293, M-2327.—Numerous alkylations were carried out, under varying conditions, in the course of the preparation of a sufficient quantity (about 15 g.) of the once promising M-2293 for initial biological documentation.

(15) Kindler, *Ann.*, **452**, 103 (1927).

(16) W. S. Johnson and Offenhauer, THIS JOURNAL, **67**, 1045 (1945).

(17) Ranedo and Leon, see *Chem. Zentr.*, **95**, I, 769 (1924).

(18) Baeyer, *Ann.*, **245**, 173 (1888).

(19) Knoevenagel and Bergdolt, *Ber.*, **36**, 2860 (1903).

(20) Compare Kharasch, Jensen and Urry, *J. Org. Chem.*, **10**, 386 (1945).

TABLE B

YIELDS OF ISOMERIC QUINONES

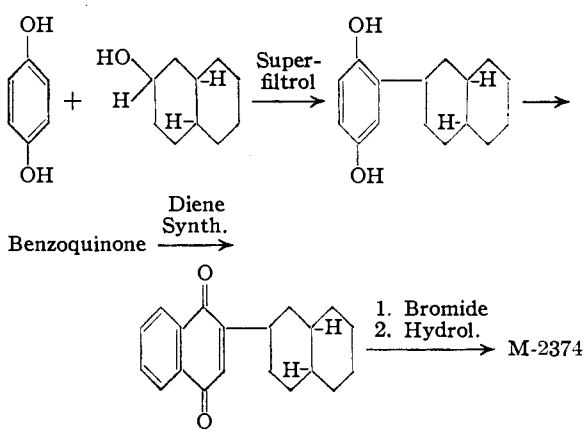
Acid used for alkylation	Peroxide, %	High-melting isomer No. or m. p.	High-melting isomer Yield, %	Low-melting isomer No. or m. p.	Low-melting isomer Yield, %
$C_6H_{11}\cdot C_6H_{10}CO_2H$, Ni.-mixt.	78	M-2293	6.2	M-2327	1.1
$C_6H_{11}\cdot C_6H_{10}CO_2H$, Pt-mixt.	79	M-2293	2.3	M-2327	0.8
trans-$C_6H_{11}\cdot C_6H_{10}CO_2H$	66	M-2293	4.9	M-2327	0.5
trans-Hexahydro-*p*-toluic acid[a,b] (m. p. 110–112°)	79	132–133°[c]	1.8	95.5–96.5[d]	2.0
"*cis*"-Hexahydro-*p*-toluic acid[a,b,f] (b. p. 90–92° (0.5 mm.), $n^{25}D$ 1.4579)	66	132–133°	0.5	94–95°	0.6
trans-Hexahydro-*o*-toluic acid[a] (m. p. 51–52°)	22	111.8–112.8°[f]	4.3		
cis-Hexahydro-*o*-toluic acid[a] (b. p. 90–91° (0.9 mm.), $n^{25}D$ 1.4619)	32	112.5–113.5° (no depression)	5.1		

[a] Skita, *Ann.*, **431**, 24 (1923). [b] Keats, *J. Chem. Soc.*, 2003 (1937). [c] Calcd. for $C_{17}H_{18}O_2$: C, 75.53; H, 6.71. Found: C, 75.56; H, 6.95. [d] Found: C, 75.76; H, 6.84. [e] Willstätter and Jaquet, *Ber.*, **51**, 777 (1918). [f] Found: C, 75.35; H, 6.83.

It was found expedient to use potassium hydroxide rather than sodium hydroxide in the preparation of the peroxide by the hydrogen peroxide method, and with this improvement the yield of peroxide varied from 56 to 78%. The most successful alkylation (M. F.) was one conducted with peroxide (78% yield) from 50 g. of the chloride of the acid mixture obtained by nickel hydrogenation. The reaction mixture on cooling deposited crystalline material that when washed with soda in ethereal solution (residue from the ether: 1.4 g. m. p. 190–193°) and crystallized twice from alcohol gave a first crop of 1.2 g. of pure *trans* quinone M-2293. A second crop was obtained by adding 20 cc. of water to the acetic acid mother liquor (350 cc.) and processing the crystallizate as before. This material (1.3 g., m. p. 175–185°) was contaminated with starting acid but was easily purified by extraction with petroleum ether, in which the acid is almost insoluble; the pure M-2293 amounted to 1.1 g., m. p. 194.5–195.5°; total yield from peroxide, 2.3 g. (6.2%). The acetic acid mother liquor was then evaporated and processed according to method (a); in the soda extraction the salt of the starting acid separated as a solid at the interface and was separated by filtration. The crude quinone (3.6 g., 135–155°) on two crystallizations from methanol yielded 1.2 g. of nearly pure *cis* isomer, m. p. 159–161°; this was purified through the acetate, which forms heavy prisms easily separated from a crop of fine needles (m. p. 122–135°) that crystallized from alcohol after the prisms. Hydrolysis of the acetate afforded pure M-2327, m. p. 166–166.5°; yield 0.40 g. (1.1%). In no other of several alkylations conducted by the same and other experimenters was the yield of M-2293 as high, and it was usually about 1–2%. Table B shows that there is no advantage in the use of the pure *trans* acid or the mixtures resulting from hydrogenation over either nickel or platinum and that both isomeric quinones were produced starting with a sterically pure acid. Table B also summarizes the results of alkylations with the *cis* and *trans* isomers of hexahydro-*p*- and *o*-toluic acid; in the first instance, both the *cis* and *trans* acids yielded a high-melting quinone that seemed fully homogeneous (hydroquinone triacetate, m. p. 189.2–190°) and a low-melting isomer that may not be fully pure (hydroq. triacet., m. p. 166–172°).

Isomeric 2-Hydroxy-3-decalyl-1,4-naphthoquinones (C. H.)

The intermediates employed in the synthesis of M-2828 and M-2374 are listed in Table C. M-2828, obtained in only 1.9% yield by peroxide alkylation with the acid mixture resulting from Pt-hydrogenation of β-naphthoic acid, appears to be a homogeneous *cis*-decalyl isomer. M-2374 was synthesized from pure trans-β-decalol kindly provided by the NDRC group of Dr. Homer Adkins. As in a patented procedure for conducting related alkylations,[21] a mixture of 75 g. of hydroquinone, 51.5 g. of *trans*-β-decalol, and 8 g. of Superfiltrol[22] was heated to 145°, when water began to be formed, and stirred mechanically with increase in the temperature to 165° in one-half hour, when the theoretical amount of water had been collected in a take-off. Heating was continued for one hour longer and the cooled mixture was extracted with acetone and the filtered solution poured into 500 cc. of water. 2-*trans*-β-Decalylhydroquinone separated as a hard glass that failed to crystallize even after being distilled (large residue). The substance is completely insoluble in aqueous alkali (see Table C for data). For oxidation, 31.3 g. of the hydroquinone was added to a solution at 65° of 67 g. of ferric chloride hexahydrate in 100 cc. of acetic acid and 50 cc. of 36% hydrochloric acid and the solution heated briefly on the steam-bath and poured into a warm solution of 21 g. of chromic oxide and 68 cc. of 96% sulfuric acid in 1.4 l. of water. The quinone extracted with ether and crystallized once from methanol (m. p. 100–103°) was used in the next step, although four recrystallizations were required before a sample was satisfactory for analysis. The diene synthesis was conducted as in Paper III but the intermediates failed to crystallize and the naphthoquinone was obtained in a satisfactory state only on repeated crystallization. An oily batch of quinone was brominated in the presence of sodium acetate, and extensive purification was required at this stage and after hydrolysis with methanol-sodium hydroxide as in Paper III (20% yield).



Search for an Alternate Method of Alkylation (F. C. C., M. G. E., L. F. F., A. G. W., E. W.).—Table D summarized the few definitive results of an extensive program of research conducted in the hope of developing an alkene or alkanol alkylation procedure that would provide a prac-

(21) Perkins to Dow Chemical Co., U. S. Patent 2,125,310 (1936).

(22) Fine mesh catalyst calcined, X365C (Filtrol Corp., Los Angeles).

TABLE C

INTERMEDIATES

Compound	Formula	Method	Yield, %	M. p. or b. p., °C.	Mm.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
		M-2828							
Decalin-β-carboxylic acid (*cis* mixture)	$C_{11}H_{18}O_2$	Pt-hydrog. of β-naphthoic acid in HOAc, cryst. from lig.	61	m 79–82		72.49	71.54	9.95	10.13
Chloride		$SOCl_2$	90	b 90–93	1				
		M-2374							
2-*trans*-β-Decalylhydroquinone	$C_{16}H_{22}O_2$	Alkylation of hydroquinone	48	b 185–195	0.5	78.01	78.11	9.00	9.45
2-*trans*-β-Decalyl-1,4-benzoquinone	$C_{16}H_{20}O_2$	Oxidn.	44	m 140–142		78.65	78.44	8.25	8.46
2-*trans*-β-Decalyl-1,4-naphthoquinone	$C_{20}H_{22}O_2$	Diene synthesis	Low	m 95–98		81.60	81.54	7.54	7.82
2-Bromo-3-*trans*-β-decalyl-1,4-naphthoquinone	$C_{20}H_{21}O_2Br$	Br_2, HOAc, NaOAc	35	m 148.5–150		64.34	64.92	5.67	5.99

tical route to cycloalkyl derivatives of the type of M-2293. Where no indication of the yield is given, the yield usually was extremely low. Usually experiments were conducted first with cyclohexene or cyclohexanol and then with the cyclohexylcyclohexane derivatives; the performance of the latter invariably was inferior and the products much more difficult to isolate and characterize. The alkylation of hydroquinone or an O-alkyl derivative is attended with the difficulty that disubstitution always occurs to a considerable extent, although the result reported in the preceding section shows that a yield up to 48% is possible with the use of the excellent Friedel–Crafts catalyst Superfiltrol. A serious obstacle to efficient C-alkylation of a naphthohydroquinone seems to be the ready formation of O-alkyl derivatives; attempts to prepare and rearrange such ethers were disappointing. The alkylation of the corresponding methyl ethers was accomplished in moderate yield but the alkylated ethers resisted hydrolysis. Hydrogen fluoride effects an interesting partial hydrolysis of 1,2,4-triacetoxynaphthalene, but no way was found for utilizing the product in a synthesis. It was found possible to condense 2,3-dichloro-1,4-naphthoquinone with 2-

TABLE D

ALKYLATION EXPERIMENTS

Hq = Hydroquinone. C_6H_{10} = Cyclohexene. NQ = 1,4-Naphthoquinone. NHq = 1,4-Naphthohydroquinone. $C_6H_{11}OH$ = Cyclohexanol. Cy_2 = 4′-Cyclohexylcyclohexyl. N = Naphthalene. CCP = 2-Carbethoxycyclopentanone.

Components	Conditions	Product	M. p. or b. p. °C.	Mm.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
Hq + C_6H_{10}	HF, 5 hr., 0°	$(C_6H_{11})_2$-Hq	m 228–229		$C_{18}H_{26}O_2$	78.79	78.88	9.55	9.77
		Diacetate	m 201–202		$C_{22}H_{30}O_4$	73.71	74.07	8.44	8.66
Hq di-Me ether + C_6H_{10}	$AlCl_3$, $CHCl_2CHCl_2$, 25°	Dimethyl ether	m 162–162.5		$C_{20}H_{30}O_2$	79.42	79.47	10.00	10.25
NHq + C_6H_{10}	HF, 15 hr., 0°	C_6H_{11}-NQ	m 88–89		$C_{16}H_{16}O_2$	79.97	80.12	6.71	6.96
NHq + $C_6H_{11}OH$	BF_3 gas, 90°	C_6H_{11}-NQ	m 81–83						
NHq + $(CH_3)_2CHOH$	BF_3 gas, 80°	NHq mono ether	m 94–95		$C_{12}H_{14}O_2$	77.22	76.86	6.98	6.66
Rearr. of ether	BF_3, *i*-PrOH, 80°	2-*i*-Propyl-NHq	dec. 184–186		$C_{12}H_{14}O_2$	77.22	77.70	6.98	6.46
NQ + $(Cy_2CO_2)_2$	HOAc, 90°	2-*trans*-Cy_2-NQ[a]	m 137.5–138.5		$C_{22}H_{28}O_3$	81.95	82.17	8.13	8.27
2-Cl-NQ + $(Cy_2CO_2)_2$	HOAc, 90°	2-Cl-3-Cy_2NQ[b]	m 208.5–209.5		$C_{22}H_{25}O_2Cl$	74.04	74.18	7.06	7.41
α-Naphtbol + Cy_2OH	Superfiltr., 160°	2-*trans*-Cy_2-1-naphthol[c]	m 188–189		$C_{22}H_{28}O$	85.66	85.49	9.15	9.15
α-Naphtbol + Cy_2OH	BF_3–Etherate, 90°								
	(a) neutral	Cy_2O-Naphthyl	b 230–240	0.4	$C_{22}H_{28}O$	85.68	85.50	9.15	9.28
	(b) Claisen alk. ext.	2-*trans*-Cy_2-1-naphthol	m 184–186		$C_{12}H_{14}O_2$				
2-Cl-NHq + C_6H_{10}	HF, 4 hr., 0°	2-Cl-3-C_6H_{11}-NQ	m 150–152		$C_{16}H_{15}O_2Cl$	69.94	69.94	5.50	5.78
Hydroxy-NHq + C_6H_{10}	HF, 2 hr., 0°	(a) M-266	m 136–137						
		(b) Ether of the hydroq.	m 83–84		$C_{22}H_{28}O_3$	77.61	77.69	8.29	8.37
NHq di-Me et. + C_6H_{10}	$AlCl_3$, $CHCl_2CHCl_2$, 25°	2-C_6H_{11}-1,4-$(OCH_3)_2$-N	b 120–130	0.1	$C_{18}H_{27}O_2$	79.96	79.34	8.20	8.05
NHq di-Me et. + Cy_2OH	BF_3-Etherate, 90°	2-Cy_2-1,4-$(OCH_3)_2$-N[d]	b 150–160	1×10^{-5}	$C_{24}H_{32}O_2$	81.77	81.65	9.15	9.44
N + Cy_2OH	BF_3 gas	Cy_2-N (yield 25%)	b 185–190	0.5	$C_{22}H_{28}$	90.35	90.16	9.64	10.21
Hydroxy-NQ + $C_6H_{11}OH$	BF_3 gas, dioxane, 80°	Cy_2O-NQ	m 111–112		$C_{16}H_{16}O_3$	74.98	74.97	6.29	6.50
1,2,4-AcO-N	HF, 2 hr., 0° (80%)	1-AcO-2,4-$(OH)_2$N	dec. 219–221		$C_{12}H_{10}O_4$	66.05	65.66	4.62	4.86
2,3-Cl_2-NQ + CCP	NaOEt, dioxane, EtOH	2-Cl-3-CCP-NQ	141.5–142		$C_{18}H_{15}O_5Cl$	62.34	62.64	4.36	4.49

[a] Isolated by extraction of the hydroquinone with Claisen's alkali; bromination and hydrolysis gave M-2293. [b] Yields M-2293 on hydrolysis. [c] Plates from ligroin; HNO_3 in HOAc gave the naphthoquinone, m. p. 138°. [d] Resisted hydrolysis with pyridine hydrochloride.

TABLE E

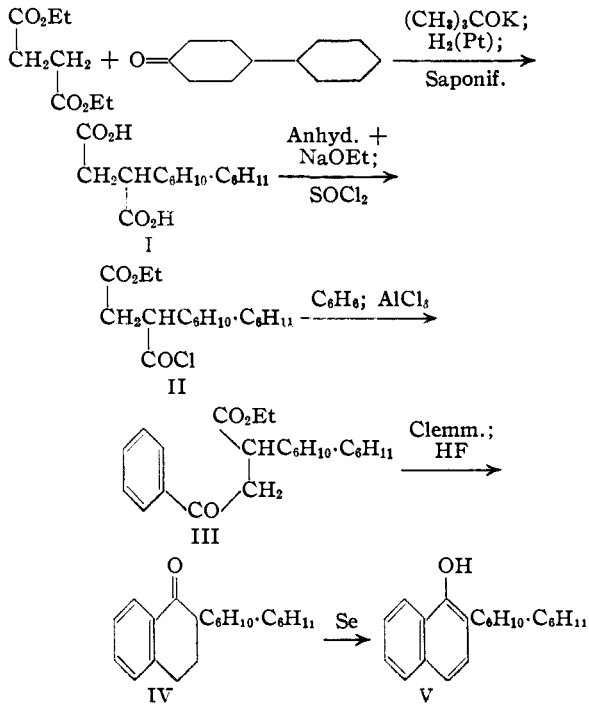
EXPERIMENTS ON SYNTHESIS BY RING-CLOSURE AND OTHER METHODS

Compound ($-C_6H_{10}\cdot C_6H_{11}$ = 4'-Cyclohexylcyclohexyl-)	Method	M. p. or b. p. °C.	Mm.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
$C_6H_{11}\cdot C_6H_{10}CN$	$RCOCl \rightarrow RCONH_2$; $SOCl_2$ (68%)	b 130–132 m 33–35	2	$C_{13}H_{21}N$	81.61	81.96	11.06	10.53
$C_6H_{11}\cdot C_6H_{10}COCH_2C_6H_5$	RCN + $C_6H_5CH_2MgCl$ in C_6H_6 (50%)	b 180–183 m 67–69	0.4	$C_{26}H_{28}O$	84.45	84.36	9.92	10.16
$C_6H_{11}\cdot C_6H_{10}CH(CO_2C_2H_5)_2$	RBr + $NaCH(CO_2R)_2$, refl. 5 days[a]	b 165–168	1	$C_{19}H_{32}O_4$	70.33	70.87	9.94	10.18
4-C_6H_{11}-cyclohexanone Azine	Attempted production of hydrazone	m 148–150		$C_{24}H_{46}N_2$	80.83	80.30	11.42	10.78
$C_6H_{11}\cdot C_6H_{10}NHCO_2C_2H_5$	(a) Curtius degradation of azide[b]	m 127–129		$C_{15}H_{27}O_2N$	71.10	70.69	10.74	10.06
	(b) Amine + $ClCO_2C_2H_2$[b]	m 126–128		$C_{15}H_{27}O_2N$		71.41		10.46
4-C_6H_{11}-cyclohexanone oxime	In EtOH (65%)[c]	m 104–105		$C_{12}H_{21}ON$	73.79	73.60	10.84	10.06
4-C_6H_{11}-cyclohexylamm. acetate	Oxime + H_2 (Pt) in HOAc	m 196–198		$C_{14}H_{27}O_2N$	69.66	69.84	11.28	11.12
$C_6H_{11}\cdot C_6H_{10}NHCOCH_3$	Acetate salt → amine; Ac_2O	m 162–163		$C_{14}H_{25}ON$	74.94	74.75	11.23	10.68
$C_6H_{11}\cdot C_6H_{10}CH(CO_2H)$-$CH_2CO_2H$	Stobbe; Pt-hydr.; saponif.[d]	m 188–189		$C_{16}H_{26}O_4$	68.05	68.26	9.28	9.66
Anhydride	CH_3COCl; reflux one hour	m 139–140		$C_{16}H_{24}O_3$	72.69	72.69	9.15	9.38
$C_6H_{11}\cdot C_6H_{10}CH(CO_2H)$-$CH_2CO_2C_2H_5$	Anhyd. + $NaOC_2H_5$ in EtOH at 0°							
Amide	Undistilled chloride + NH_3	m 193.5–194		$C_{18}H_{31}O_3N$	69.86	69.68	10.10	9.89
$C_6H_{11}\cdot C_6H_{10}CH(CO_2C_2H_5)$-$CH_2COC_6H_5$	Crude chloride + C_6H_6 + $AlCl_3$ (60%)	m 95.5–96.5		$C_{24}H_{34}O_3$	77.79	77.60	9.25	9.41
$C_6H_{11}\cdot C_6H_{10}CH(CO_2H)$-$CH_2COC_6H_5$	From alkaline extract	m 170–173		$C_{22}H_{30}O_3$	77.15	77.47	8.83	9.10
2-(4'-$C_6H_{10}\cdot C_6H_{11}$)-tetralone-1	Clemm.-Martin red. (70%), HF[e]	m 121–123		$C_{22}H_{30}O$	85.11	85.26	9.74	9.60

[a] Yield 40%; $n^{25}D$ 1.4733; alkylation unsuccessful. [b] Identical; attempted conversion to nitroso compound negative. [c] Calcd. N, 7.17; found N, 7.42. [d] Procedure of W. S. Johnson, Goldman and Schneider, THIS JOURNAL, 67, 1358 (1945); di-acid separated as sparingly soluble sodium salt in 30% over-all yield. [e] Dehydrogenation with selenium gave 2-*trans*-4'-cyclohexylcyclohexyl-1-naphthol, m. p. 187–188°, identical with that of Table D.

carbethoxycyclopentanone, but the yield was low (25%), the product could not be hydrolyzed, and the condensation failed with the keto esters from cyclohexane and cyclohexylcyclohexane. Peroxide alkylation of both 1,4-naphthoquinone and its 2-chloro derivative was accomplished with the reagent from 4-cyclohexylcyclohexanecarboxylic acid and each quinone was converted into M-2293, but neither process offers any advantages over alkylation of the hydroxy compound. The best present route to M-2293, however, is by synthesis of the next higher homolog and Hooker oxidation (Paper XII).

Attempted Synthesis by Ring-Closure and Other Methods (C. H.).—Notes on new compounds prepared in the course of the trial of several synthetic approaches are given in Table E and require but little explanation; the known ring-closure syntheses after which some of the trials were planned are discussed in Paper IV. The second and third entries in the table illustrate the very great hindrance exerted by the 4-cyclohexylcyclohexyl group; the ketone could not be forced to undergo a Reformatsky reaction nor the malonic ester to undergo alkylation with either phenylethyl bromide or ethyl bromoacetate. Two methods were tried for the synthesis of the diazo derivative of 4-cyclohexylcyclohexane but both failed; attempted preparation of the hydrazone gave the azine, and the urethan, prepared in two ways, failed to react with nitrous acid. A synthesis planned to proceed through 3-($C_6H_{11}\cdot C_6H_{10}$)-tetralone-1 failed for an unexpected reason. The dibasic acid I was obtained by Stobbe–Johnson condensation and saturation of the double bond of the initial product, and it was converted by known methods into a half-ester acid chloride that must have the structure II. When this was submitted to Friedel–Crafts reaction with



benzene, however, an exchange evidently occurred with attachment of the aryl radical to the unhindered carbonyl group to give III, for the α-tetralone derived from it failed to condense with *p*-nitrosodimethylaniline or with selenium dioxide, and on dehydrogenation with selenium it afforded a product identical with the 2-(*trans*-4′-cyclohexylcyclohexyl)-1-naphthol described in Table D. An analogous exchange reaction has been observed by Sengupta.[23]

Summary

The configurations of the *cis* and *trans* isomers of the series 4′-cyclohexyl-cyclohexyl-$(CH_2)_n$-CO_2H, where n = 0, 1, 2 and 3, and of the series C_6H_5-cyclohexyl-$(CH_2)_n$-CO_2H, where n = 0 and 1, and of the quinones obtained from them by peroxide alkylation have been established. When the carboxyl group of an acid is attached directly to a center involved in geometrical isomerism, the original configuration is not retained in the peroxide alkylation reaction.

Attempts to develop an efficient process for the synthesis of the highly potent compounds having a cycloalkyl group linked directly to the quinone ring met with little success. The best general method of preparation is by Hooker oxidation of the next higher homolog.

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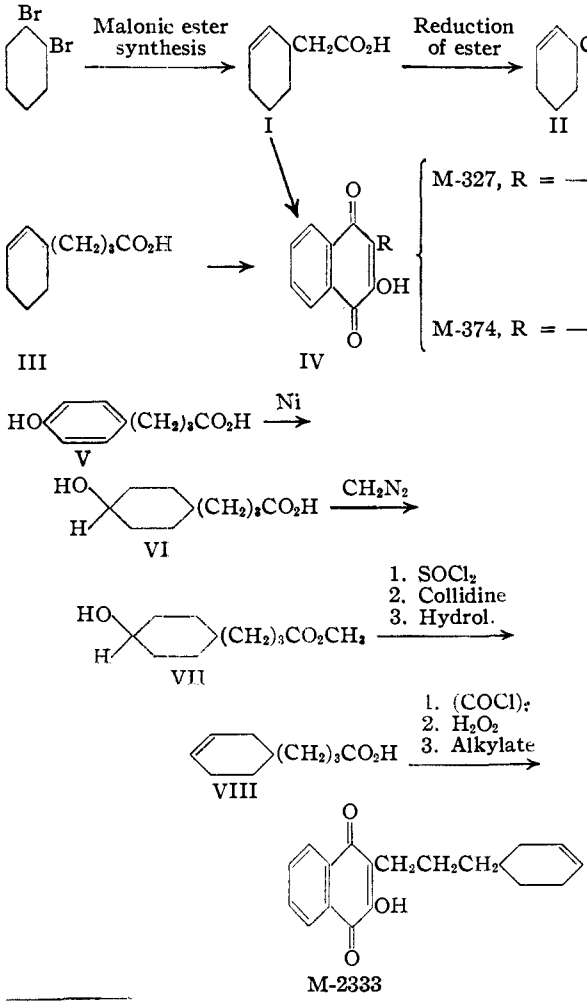
(23) Sengupta, *J. prakt. Chem.*, **151**, 82 (1938).

Naphthoquinone Antimalarials. IV–XI. Synthesis. VII. Unsaturated Compounds

The first two of the new unsaturated quinones synthesized were obtained from the known Δ²-cyclohexenylacetic acid[1] (I)



(1) Eijkman, *Chem. Weekblad*, **6**, 699 (1909) [*Chem. Zentr.*, **80**, II, 2146 (1909)].

This was used for peroxide alkylation to give 2-hydroxy - 3 - (Δ²′ - cyclohexenylmethyl) - 1,4 - naphthoquinone (M-327), and was converted to the higher homolog III for alkylation to M-374. The properties of the quinones and intermediates are listed in Table X and A.

M-374 is the Δ²′-dehydro derivative of M-1916. The Δ³′-dehydro isomer M-2333 was synthesized by the sequence of reactions indicated in the formulas. Some of the transformations required special conditions, as outlined in the Experimental Part. The fourth and fifth members of this series, M-289 and M-1945, were obtained by alkylation with the peroxides from undecylenic and chaulmoogric acids. In none of the five instances cited was any difficulty experienced in the preparation and utilization for alkylation of the peroxides of the unsaturated acids. The situation is distinctly less favorable, however, with α,β-unsaturated acids. Thus peroxides were obtained in 40–80% yield from crotonic, cinnamic and *o*- and *p*-bromocinnamic acid, but no products could be isolated

TABLE X

UNSATURATED QUINONES

M-	Formula	M. p., °C.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
327[a]	$C_{17}H_{16}O_3$	145–145.5	76.10	76.59	6.01	6.18
374[b]	$C_{19}H_{20}O_3$	139–140	77.00	76.90	6.80	6.96
2333[c]	$C_{19}H_{20}O_3$	124–125	77.00	77.05	6.80	6.69
289[d]	$C_{20}H_{24}O_3$	70–71	76.89	77.04	7.74	7.76
1945[e]	$C_{27}H_{36}O_3$	66–67	79.37	79.50	8.88	9.02
Acet.	$C_{29}H_{38}O_4$	68–69	77.30	76.86	8.50	8.45

[a] K. E. H. with D. L. Tabern. [b] E. E. M. [c] W. G. D. at the University of California at Berkeley; analysis by C. W. Koch. [d] K. E. H. [e] W. G. D.

TABLE A

INTERMEDIATES

Compound	Formula	Method	Yield, %	$n^{25}D$	M. p. or b. p. °C.	Mm.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
Ethyl Δ^2-cyclohexenylacetate		From known acid	65	1.4565	b 105–107	9				
2-Δ^2-Cyclohexenylethanol	$C_8H_{14}O$	Na-Alc. redn. of ester	82	1.4722	b 74–75	2	76.14[a]	76.53	11.18	11.43
Bromide		PBr_3	65	1.5052	b 150	22				
Malonic ester		From bromide	60	1.4625	b 140–150	2				
Malonic acid	$C_{11}H_{16}O_4$	Hydrol.			m 114–116		62.25	62.50	7.60	7.67
γ-Δ^2-Cyclohexenylbutyric acid	$C_{10}H_{16}O_2$		83	1.4752	b 128–132	2	71.39	71.63	9.59	9.48
Chloride		$SOCl_2$ in CCl_4	67		b 100–102	2				
γ-4-Hydroxyphenylbutyric acid	$C_{10}H_{12}O_3$	Me-ether + HBr	76		m 107–108		66.63	66.48	6.71	6.43
Acetate	$C_{12}H_{14}O_4$	Ac_2O, H_2SO_4	53		b 163–164	0.5[b]	64.85	65.12	6.35	6.61
γ-4-Hydroxycyclohexylbutyric acid	$C_{10}H_{18}O_3$	Ni-hydrog.	75		m 118–120		64.49	64.44	9.74	9.93
Methyl γ-4-hydroxycyclohexylbutyrate	$C_{11}H_{20}O_3$	CH_2N_2	86	1.4705	b 101–103	0.2	65.97	66.10	10.09	10.33
Methyl γ-Δ^3-cyclohexenylbutyrate	$C_{11}H_{18}O_3$	$SOCl_2$; collidine	76	1.4638	b 67–70	0.5	72.49	72.30	9.95	10.03
γ-Δ^3-Cyclohexenylbutyric acid	$C_{10}H_{16}O_2$	Refl. with 10% NaOH	87.5	1.4785	b 105–106	0.2	71.39	71.49[c]	9.59	9.37
p-Phenylphenacyl ester	$C_{24}H_{26}O_3$				m 65.5–66		79.52	79.79	7.23	7.45
Chloride		$(COCl)_2$ at 70°	93.5		b 67–69	0.5				

[a] Iodine no., calcd. 196, found 200. [b] M. p. 62.5–63.5°. [c] Analysis by C. W. Koch.

from attempted alkylation with these peroxides of either 2-hydroxy- or 2-methyl-1,4-naphthoquinone (M. W.). Δ^1-Cyclohexenylbutyric acid was converted successfully to the acid chloride with oxalyl chloride and the peroxide was obtained in yields of 55 and 65%, but in two experiments this failed to react with hydroxynaphthoquinone (E. E. M.).

Experimental

Notes on the Synthesis of M-2333.—γ-4-Hydroxyphenylbutyric acid was prepared by heating a suspension of γ-(*p*-anisoyl)-butyric acid[2] (230 g.) in 48% hydrobromic acid (230 cc.) under reflux until a solution (slightly turbid) resulted; the product crystallized on cooling as a solid cake on top of the aqueous layer and this was ground, washed with water, dried and crystallized from benzene. The first attempts to hydrogenate this phenolic acid or a derivative led to the elimination of the hydroxyl function; this happened, in whole or in part, on hydrogenation of the acetate with Adams catalyst in acetic acid or of the methyl ether over Raney nickel in methanol at 150°. A successful process consisted in hydrogenating 94 g. of the free hydroxy acid in a solution of 27.5 g. of sodium carbonate in 200 cc. of water over 25 cc. of settled Raney nickel at an initial pressure of 2500 lb./sq. in. (25°); the theoretical amount of hydrogen was absorbed in about twenty-four hours. Acidification of the filtered solution gave an oil that slowly set to a solid (86.5 g.); this afforded material satisfactory for the next step on one crystallization from benzene. Material extracted from the aqueous liquor appeared to be a mixture of the desired product with either starting material or the product of hydrogenolysis (C, 63.47; H, 9.65). The next step, the conversion of the acid to the methyl ester, was best done with diazomethane. The route through the silver salt and methyl iodide in boiling methanol (twelve hours) gave the same product in only 53.5% yield, the esterification by the Fischer method or with acetyl chloride as catalyst gave still poorer results.

Dehydration was accomplished most satisfactorily by heating 42 g. of the ester with 31 cc. of purified thionyl chloride and 60 cc. of benzene on the steam-bath for six hours (conversion to chloride), evaporating in vacuum, and heating the residue with 50 cc. of 2,4,6-collidine at 150° for four hours. The product was isolated in good yield by ether extraction and distillation. Pyridine effected only a partial elimination of hydrogen chloride, and dehydration of the hydroxy ester over potassium bisulfate was likewise incomplete; the free acid under similar conditions yielded chiefly a neutral product. The unsaturated acid (25 g.), obtained by refluxing the ester with 10% aqueous alkali for three hours, was converted smoothly to the acid chloride by letting it stand with oxalyl chloride (56.5 g.) until the gas evolution subsided and then warming the mixture at 70° for four hours; the excess reagent was then removed in vacuum and the product distilled. Alkylation proceeded as usual.

Alkylation with Dichaulmoogryl Peroxide (M-1945).—Ethyl chaulmoograte (66 g.) was shaken with alkali under pressure at 100°[3] and the resulting acid crystallized from absolute alcohol (164 cc.) diluted, after clarification with Norit, with water (36 cc.); 43 g. (72%) of white plates, m. p. 62–63°. The acid chloride,[4] prepared with phosphorus trichloride, decanted, and digested with petroleum ether which was then evaporated, yielded a nicely crystalline peroxide. After alkylation, the solvent was removed and the residue sublimed at 0.5 mm. from a bath at 130–

(2) Fieser and Hershberg, THIS JOURNAL, **58**, 2315 (1936); Martin, *ibid.*, **58**, 1439 (1936).

(3) Shriner and Adams, THIS JOURNAL, **47**, 2727 (1925).

(4) Hinegardner and Johnson, *ibid.*, **51**, 1503 (1929).

160°. White crystals of chaulmoogric acid sublimed first, followed by 11 g. of yellow material that proved to be a mixture of quinone and acid. A separation was accomplished first by a combination of fractional sublimation and crystallization. A more satisfactory method was by acetylation of the mixture, removal of the acid by soda extraction from ether, crystallization of the acetate recovered from the neutral fraction, and hydrolysis.

Summary

The peroxide alkylation reaction proceeds satisfactorily with the peroxides of acids having a double bond elsewhere than in the α,β-position.

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Naphthoquinone Antimalarials. IV–XI. Synthesis. VIII. Aralkyl and Substituted Aralkyl Series[1]

Tables XII and XIII list all the new 3-aralkyl derivatives of 2-hydroxy-1,4-naphthoquinone, and the next set of Tables include all the O-, Hal.-, and N-substituted aralkyl derivatives listed in the assay Tables XV–XVII.

Most of the quinones were made by peroxide alkylation, and the only serious limitation of the reaction encountered in this series is in the synthesis of compounds with benzyl-type substituents. Thus peroxides were obtained from phenylacetic acid, *o*-chloro- and *p*-iodophenylacetic acid, and α-naphthylacetic acid, but no substituted quinones could be obtained in attempted alkylations. On the other hand, the peroxide from *p*-nitrophenylacetic acid proved to be as satisfactory an alkylating agent as the typical peroxides. The other benzyl-type compounds are best made by Hooker oxidation of the next higher homolog.

The great majority of the acids required as intermediates were prepared by Friedel–Crafts reaction of an aromatic substance with the cyclic anhydride or half-ester acid chloride of a dibasic acid and reduction of the resulting keto acid. Most of the reductions were carried out by the Clemmensen method according to Martin's procedure[1a] as further improved by Sherman[2] by the introduction of stirring and the use of freshly poured zinc (with great reduction in the reaction time). The convenient Wolff–Kishner procedure of Huang-Minlon[3] became available only after most of the work had been completed.

The 2-hydroxy-3-ω-phenylalkyl-1,4-naphthoquinones, with the side chain $-(CH_2)_nC_6H_5$, are now known from $n = 1$ to 9. Melting point relationships in this series may be obscured by the fact that some of the compounds behave peculiarly on crystallization and show signs of polymorphism (Paper XII). The present observations disclose alternation in only the limited range where $n = 3$, 4, 5 and 6, the respective melting points being 134, 98, 127.5 and 92°. In the series of quinones with the side chain $-(CH_2)_n\text{-}C_6H_4OC_6H_5\text{-}p$, alternation in melting point occurs where $n = 2$, 3, 4 and 5, as follows: 129, 109.6, 140 and 114.3°; here the higher melting homologs are those with an even, rather than an odd, number of methylene groups.

Acknowledgments.—We are greatly indebted to Dr. R. C. Elderfield and his CMR research group for supplies of tetrahydrophenanthrene, glutaric anhydride, cholanic acid and a quantity of mixed α- and β-naphthoylpropionic acids; to Dr. G. E. Coleman and his group for quantities of ethyl hydrogen adipate and sebacate; to Dr. Erich Mosettig and Lady Esther, Inc., for phenanthroic acids and intermediates; and to Dr. C. S. Sherman and collaborators for a supply of *p*-chlorophenylmercaptoacetic acid.

Experimental Part

Known intermediates employed for the synthesis of aralkyl and substituted aralkyl derivatives, respectively, are listed in Tables A and B, and the properties and analyses of new intermediates of both series are recorded in Table C. Supplementary notes on general and special procedures are recorded in the following paragraphs. The synthesis of M-368 was accomplished by a special method to be reported separately.

β-Arylpropionic Acids.—The intermediates required for the synthesis of M-2289 were prepared conveniently as follows: A mixture of 35 g. of *p*-chlorobenzaldehyde, 26 g. of malonic acid and 5 cc. of pyridine was heated for two hours on the steam-bath and the reaction mixture diluted with water, acidified, and the solid product collected and crystallized once from acetic acid; yield of *p*-chlorocinnamic acid, m. p. 240–242°, 33.3 g. (73.2%). Since the acid is very sparingly soluble in the common solvents, reduction was accomplished by shaking a suspension of 57 g. of acid in 300 cc. of absolute alcohol containing 6 cc. of 36% hydrochloric acid with 0.8 g. of Adams catalyst and hydrogen. The acid rapidly went into solution in the form of the ester and the calculated amount of hydrogen was consumed in two hours. The yield of *p*-chlorohydrocinnamic acid, isolated after saponification and crystallized once, was nearly quantitative.

Succinoylation.—The succinoylation of benzene and toluene was conducted efficiently with use of an excess of the hydrocarbon as solvent.[4] The corresponding reactions with chloro- and bromobenzene were carried out in carbon bisulfide solution in order to conserve the more expensive aromatic component, but the yields were less favorable. The succinoylation of solid or rare aromatic hydrocarbons and of aryl ethers was conducted best in nitrobenzene–tetrachloroethane mixtures with the use of one and two moles of aluminum chloride, respectively.[5] The preparation of the β-*p*-phenoxyphenylbutyric acid is described in detail by Huang-Minlon[3]; in this and other Friedel and Crafts substitutions of diphenyl ether, benzene proved to be a particularly satisfactory solvent.

(1) A considerable part of this work was done by Ernst Berliner and Frances J. Bondbus at the Chemical Laboratory, Bryn Mawr College.

(1a) Martin, THIS JOURNAL, **58**, 1438 (1936).

(2) Private communication from Dr. C. S. Sherman.

(3) Huang-Minlon, THIS JOURNAL, **68**, 2487 (1946).

(4) Martin and Fieser, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 82, Note 4.

(5) Fieser and Hershberg, THIS JOURNAL, **58**, 2314 (1936).

TABLES XII–XIII

2-HYDROXY-3-ARALKYL-1,4-NAPHTHOQUINONES

M-	3-Side chain	Formula	M. p., °C.	Prepd. by	Method[a]	Yield,[b] %	Solv.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
	Table XII. (a) ω-Phenylalkyl Series and (b) Polyarylalkyl Series										
1946	$-(CH_2)_2C_6H_5$ (Known)	$C_{18}H_{14}O_2$	173–174	E. B.	PA	43	Lig.	77.68	77.85	5.07	5.20
1955	$-(CH_2)_4C_6H_5$ (Known)	$C_{19}H_{16}O_2$	133–134	E. B.	PA	54	EtOH	78.06	77.99	5.52	5.55
2286	$-(CH_2)_4C_6H_5$	$C_{20}H_{18}O_2$	97–98	C. H.	PA	45	MeOH	78.41	78.65	5.92	6.10
2276	$-(CH_2)_5C_6H_5$	$C_{21}H_{20}O_2$	126.5–127.5[c]	C. H., F. J. B.	PA	38	Lig., EtOH	78.72	78.75	6.29	6.01
2387	$-(CH_2)_6C_6H_5$	$C_{22}H_{22}O_2$	92	L. F. F.	IHO			79.01	79.15	6.63	6.55
2386	$-(CH_2)_7C_6H_5$	$C_{23}H_{24}O_2$	86–87	L. F. F.	IHO			79.28	79.63	6.94	6.78
2382	$-(CH_2)_8C_6H_5$	$C_{24}H_{26}O_2$	88	L. F. F.	IHO			79.52	79.50	7.23	7.31
2301	$-(CH_2)_9C_6H_5$	$C_{25}H_{28}O_2$	78–79[c]	E. B.	PA	28	Lig.	79.75	80.10	7.50	7.63
2282	$-CH_2CH(C_6H_5)_2$	$C_{24}H_{18}O_2$	173–174	A. G. W.	PA[d]	25		81.34	81.50	5.12	5.14
2274	$-CH_2CH(C_6H_5)C_6H_4CH_3$-*p*	$C_{25}H_{20}O_2$	174.2–175	E. W.	PA	11	EtOH	81.50	81.61	5.47	5.61
1002	$-CH_2CH_2CH(C_6H_5)_2$	$C_{25}H_{20}O_2$	191.4–192.2	E. W.	PA	12	Aq. HOAc	81.50	81.27	5.47	5.71
2314	$-CH_2CH(C_6H_4CH_3$-*p*$)_2$	$C_{26}H_{22}O_2$	197.4–198.4	E. W.	PA	28	EtOH	81.66	82.01	5.80	6.08
2283	$-CH_2CH(C_6H_5)C_6H_3(CH_3)_2$-2,4	$C_{26}H_{22}O_2$	203.2–204.2	E. W.	PA	25	Aq. HOAc	81.66	81.90	5.80	5.99
2297	$-(CH_2)_2CH(C_6H_4)C_6H_4CH_3$-*p*	$C_{26}H_{22}O_2$	155.2–156.2	E. W.	PA	26	EtOH	81.66	81.37	5.80	5.77
	Table XIII. Other Aralkyl Compounds										
2234	$-(CH_2)_3C_6H_4CH_3$-*p*	$C_{19}H_{18}O_2$	191.9–193.2	F. J. B.	H	36	EtOH–C_6H_6	78.06	77.94	5.52	5.76
2281[e]	$-(CH_2)_2CH(CH_3)C_6H_5$	$C_{20}H_{18}O_2$	73–74.5	A. G. W.	PA	49		78.41	78.62	5.92	5.87
1952	$-(CH_2)_3C_6H_4CH_3$-*p*	$C_{20}H_{18}O_2$	153.5–154.5	E. B.	PA	40	EtOH	78.41	78.30	5.92	6.02
	Acetate	$C_{22}H_{20}O_4$	100.4–101.4				Aq. HAOc	75.84	75.97	5.80	6.15
2236	$-(CH_2)_2C_6H_3(CH_3)_2$-2,4	$C_{20}H_{18}O_2$	171.6–172.3	E. B.	H	40	EtOH	78.41	78.94	5.92	6.20
1003	$-(CH_2)_2C_6H_3(CH_3)_2$-2,5	$C_{20}H_{18}O_2$	183–185	E. B.	H	Low	EtOH	78.41	78.12	5.92	6.18
2235	$-(CH_2)_2C_6H_4C_2H_5$-*p*	$C_{20}H_{18}O_2$	136.2–137	E. B., F. J. B.	H	54	EtOH	78.41	78.88	5.92	6.09
2216[e]	$-CH_2CH(C_6H_5)C_6H_4$	$C_{20}H_{18}O_2$	126.5–127.5	A. G. W.	PA	48		78.41	78.57	5.92	6.20
2214	$-(CH_2)_3C_6H_3(CH_3)_2$-2,4	$C_{21}H_{20}O_2$	114.2–115.2	E. B.	PA	27	EtOH	78.72	78.65	6.29	6.26
2237	$-(CH_2)_3C_6H_3(CH_3)_2$-2,5	$C_{21}H_{20}O_2$	143.2–144.2	E. B.	PA	26	EtOH	78.72	78.85	6.29	6.55
2308	$-(CH_2)_3C_6H_3(CH_3)_2$-3,4	$C_{21}H_{20}O_2$	121–121.6	E. B.[f]	PA	28	EtOH	78.72	78.38	6.29	6.43
2230[e]	$-CH_2CH(CH_3)CH_2CH_2C_6H_4$	$C_{21}H_{20}O_2$	95–96.5	A. G. W.	PA	37		78.72	79.01	6.29	6.50
2209	$-(CH_2)_3C_6H_4C_2H_5$-*p*	$C_{21}H_{20}O_2$	119.5–120	E. B.	PA	38	EtOH	78.72	78.67	6.29	6.35
2277	$-(CH_2)_2$-5-hydrindyl	$C_{21}H_{18}O_2$	141.2–142.2	E. B.	H	35	EtOH	79.22	79.63	5.70	5.82
2242	$-(CH_2)_3C_6H_2(CH_3)_3$-2,4,6	$C_{22}H_{22}O_2$	139.6–140.2	F. J. B.	PA	20	EtOH	79.02	78.89	6.63	6.95
2252	$-(CH_2)_3C_6H_4CH(CH_3)_2$-*p*	$C_{22}H_{22}O_2$	117.1–117.8	F. J. B.	PA	40	EtOH	79.02	79.06	6.63	6.77
1004	$-(CH_2)_2\beta$-Naphthyl	$C_{22}H_{16}O_2$	144–145	E. B.	H	82	EtOH	80.47	80.49	4.91	5.12
2304	$-(CH_2)_2$-β-Tetralyl	$C_{22}H_{20}O_2$	128.5–129.5	A. G. W.	PA	18	MeOH	79.49	79.84	6.06	6.00
2257	$-(CH_2)_3$-5-hydrindyl	$C_{22}H_{20}O_2$	128.4–129.4	E. B.	PA	38	EtOH	79.50	79.50	6.07	6.39
2213	$-(CH_2)_3C_6H_4C(CH_3)_3$-*p*	$C_{23}H_{24}O_2$	112–113	E. B.	PA	15	Aq. EtOH	79.28	79.25	6.94	7.20
2302	$-(CH_2)_2$-C_6H_3Me(*i*-Pr)-2,5	$C_{23}H_{24}O_2$	150–151	E. B.[f]	PA	10	Lig.; EtOH	79.28	79.17	6.94	6.65
295	$-(CH_2)_3$-β-Tetralyl	$C_{23}H_{22}O_2$	120.8–122	K. E. H., E. B.	PA	26	EtOH	79.74	79.60	6.40	6.75
2254	$-(CH_2)_3$-α-Naphtbyl	$C_{23}H_{18}O_2$	151.5–153.5	W. G. D., E. B.	PA	17	MeOH; Lig.	80.68	80.84	5.30	5.26
2253	$-(CH_2)_3$-β-Napbthyl	$C_{23}H_{18}O_2$	159.5–161	E. B.	PA	25	C_6H_6, EtOH	80.68	80.75	5.30	5.66
2384	$-(CH_2)_2C_6H_4$-C_6H_5-*p*	$C_{24}H_{18}O_2$	157.5–158.5	M. F.	H	60	C_6H_6-Lig.	81.33	81.41	5.12	4.91
2295	$-(CH_2)_4$-β-Tetralyl	$C_{24}H_{24}O_2$	100.5–101.5	A. G. W.	PA	25	MeOH	79.97	80.01	6.71	6.81
1005[f]	$-CH_2CH(C_6H_5)C_6H_{13}$-*n*	$C_{24}H_{24}O_2$	116.5–117	A. G. W.	PA	49		79.52	79.76	7.43	7.23
2290	$-(CH_2)_3C_6H_4$-C_6H_5-*p*	$C_{25}H_{20}O_2$	171–172	M. F.	PA	37	C_6H_6-lig.	81.50	81.59	5.47	5.66
2359	$-(CH_2)_2C_6H_4CH_2C_6H_5$-*p*	$C_{25}H_{20}O_2$	156.5–156.8	E. B.	H	57	EtOH–C_6H_6	81.50	81.50	5.47	5.68
2261	$-(CH_2)_1$-3-Acenaphthyl	$C_{25}H_{20}O_2$	158–160.5	E. B.	PA	Low	Aq. EtOH	81.50	81.60	5.47	5.58
2323	$-(CH_2)_3C_6H_4$-Cyclohexyl-*p*	$C_{25}H_{26}O_2$	143.5–144	E. B.	PA	27	Lig.	80.18	80.19	7.00	7.30
2339	$-(CH_2)_3C_6H_4CH_2C_6H_5$-*p*	$C_{26}H_{22}O_2$	118.3–119.5	E. B.	PA	30	Lig.	81.65	81.52	5.80	5.91
2272[g]	$-(CH_2)_3$-2-Fluoryl	$C_{26}H_{20}O_2$	228–229.8	E. B.	PA	16	Toluene	82.08	82.57	5.30	5.44
2255	$-(CH_2)_3$-1,2,3,4-Tetrahydro-9-phenanthryl	$C_{27}H_{24}O_2$	167–168	C. H.	PA	18	C_6H_6-lig.	81.80	81.55	6.10	6.20
2285	$-(CH_2)_3$-α-Thienyl	$C_{17}H_{14}O_2S$	140.5–141.5	M. G. E.	PA	22	Lig.	68.44	68.43	4.73	4.68

[a] PA = Peroxide alkylation; H = Hooker oxidation; IHO = Improved Hooker oxidation. [b] Yield of pure quinone from peroxide (or acid chloride), not allowing for recovered starting material. [c] Details reported in Paper XII. [d] A neutral by-product isolated from this alkylation is a colorless solid, m. p. 141.5–142°, having the composition of the ester: $(C_6H_5)_2CHCH_2COOCH_2CH(C_6H_5)_2$. Calcd. for $C_{29}H_{26}O_2$: C, 85.68; H, 6.45. Found: C, 85.74; H, 6.72. Hydrolysis gave an acid, m. p. 154–155°, identical with β,β-diphenylpropionic acid. [e] The acid was kindly supplied by Dr. H. E. Carter; see Carter, *J. Biol. Chem.*, 108, 619 (1935). [f] With Mrs. Harvey Satenstein. [g] Intermediate prepared according to Koelsch, THIS JOURNAL, 55, 3886 (1933); our yields and melting points corresponded to his. The purification of the quinone is difficult because of the presence of a neutral by-product that is more soluble than the quinone in benzene and less soluble in acetic acid; the substance forms silvery plates from benzene, m. p. 198.6–199.6°, and appears to be a dimer of the type RR (found: C, 93.34; H, 7.13; calcd. for $C_{32}H_{30}$: C, 92.71; H, 7.29).

The procedure used in repeated large-scale preparations of β-2-ar-tetralylpropionic acid (for M-295, M-297, and M-2279) is as follows (W. G. D.): A mixture of 1 kg. (7.57 moles) of redistilled tetralin, 500 g. (5 moles) of succinic anhydride, and 1 l. of thiophene-free benzene was stirred mechanically under reflux (hydrochloric acid-trap)

TABLES XV–XVII (In Part)

SUBSTITUTED 3-ARALKYL DERIVATIVES OF 2-HYDROXYL-1,4-NAPHTHOQUINONE

M-	3-Side chain	Formula	M. p., °C.	Prepd. by	Method	Yield, %	Notes	Solv.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
				Table XV. Oxygenated side chains								
368	$-CH(C_6H_5)CH_2COCH_3$	$C_{20}H_{16}O_4$	143–144	H. E. Z.	Text		Yel. powder	Ether	74.98	74.97	5.04	5.24
2205	$-(CH_2)_3C_6H_4OCH_3$-*p*	$C_{20}H_{16}O_4$	136.8–137.8	E. B.	PA	34	Yel. needles	EtOH	74.52	74.60	5.62	6.05
2364	$-(CH_2)_3C_6H_3(OCH_3)_2$-2.5	$C_{21}H_{20}O_5$	110–112	E. B.	PA	14	Orange prisms	C_6H_6–Lig.	71.57	71.82	5.72	6.04
2363	$-(CH_2)_4C_6H_4OCH_3$-*p*	$C_{21}H_{20}O_4$	115.8–116.6	E. B.	PA	37	Yel. prisms	C_6H_6–Lig.	74.98	75.25	5.99	6.02
2357	$-(CH_2)_5C_6H_4OCH_3$-*p*	$C_{22}H_{22}O_4$	84.5–85.5	F. J. B.	PA	13	Needles	Lig.	75.41	75.55	6.33	6.54
2380	$-CH_2C_6H_4OC_6H_5$-*p*	$C_{23}H_{16}O_4$	162–163	L. F. F.	IHO[a]	87.5	Needles	Lig.	77.51	77.72	4.53	4.88
2338	$-(CH_2)_2C_6H_4OC_6H_5$-*p*	$C_{24}H_{18}O_4$	128–129	E. B., L. F. F.	H	21(91)[a]	Fine needles	EtOH	77.82	78.15	4.90	4.94
2311	$-(CH_2)_3$-2-Dibenzfuryl	$C_{25}H_{18}O_4$	154.8–156.8	F. J. B.	PA	2	Needles	EtOH	78.52	78.23	4.74	4.99
2309[b]	$-(CH_2)_3C_6H_4OC_6H_5$-*p*	$C_{25}H_{20}O_4$	108.6–109.6	E. B.	PA	31–42	Needles	MeOH	78.12	78.48	5.24	5.51
2334[c]	$-(CH_2)_9C_6H_4OCH_3$-*p*	$C_{26}H_{30}O_4$	88.5–89.5	E. B.	PA	24	Small needles	EtOH; lig.	76.82	76.57	7.44	7.30
2361[b]	$-(CH_2)_4C_6H_4OC_6H_5$-*p*	$C_{26}H_{22}O_4$	139–140	F. J. B.[d]	H[a]	56	Needles	EtOH	78.37	78.59	5.57	5.75
2345	$-(CH_2)_5C_6H_4OC_6H_5$-*p*	$C_{27}H_{24}O_4$	112.5–114.3	F. J. B.	PA	30	Long needles	EtOH	78.62	78.41	5.86	6.14
2360	$-(CH_2)_9C_6H_4OC_6H_5$-*p*	$C_{31}H_{32}O_4$	65.8–66.6	E. B.	PA	14	Irreg. cryst.	Lig.	79.46	79.54	6.89	7.03
				Table XVI. Halogenated side chains								
2201	$-CH_2C_6H_4Cl$-*o*	$C_{17}H_{11}O_3Cl$	184.4–185.2	E. B.	H[e]	78	Yield crude		68.35	68.39	3.71	4.01
1738	$-CH_2C_6H_4Cl$-*p*	$C_{17}H_{11}O_3Cl$	167–167.6	Mary F.[f]			Needles	EtOH	68.35	68.60	3.71	3.94
2202	$-CH_2C_6H_4Br$-*o*	$C_{17}H_{11}O_3Br$	181.2–181.8	E. B.	H[e]	80	Yield crude	EtOH	59.49	59.86	3.23	3.52
2366	$-CH_2C_6H_4Br$-*p*	$C_{17}H_{11}O_3Br$	171–171.7	F. J. B.	H	60	Fine needles	EtOH	59.49	59.60	3.23	3.55
1962	$-CH_2CH_2C_6H_4Cl$-*o*	$C_{18}H_{13}O_3Cl$	162.5–163	E. B.	PA	33	Golden prisms	EtOH	69.13	69.24	4.19	4.48
2289	$-CH_2CH_2C_6H_4Cl$-*p*	$C_{18}H_{13}O_3Cl$	153–153.8	F. J. B.	PA, H	43	Needles	EtOH	69.13	69.10	4.19	4.34
1968	$-CH_2CH_2C_6H_4Br$-*o*	$C_{18}H_{13}O_3Br$	160.8–161.8	E. B.	PA	39	Golden plates	EtOH	60.52	60.41	3.67	3.91
2358	$-CH_2CH_2C_6H_4Br$-*p*	$C_{18}H_{13}O_3Br$	165.5–166.2	F. J. B.	H[g]	52	Long needles	EtOH	60.52	60.81	3.67	4.04
2332	$-CH_2CH_2C_6H_4F$-*p*	$C_{18}H_{13}O_3F$	142.4–143.4	E. B.	H	45	Plates, needles	EtOH	72.97	73.12	4.42	4.47
2260	$-(CH_2)_3C_6H_4Cl$-*p*	$C_{19}H_{15}O_3Cl$	152.2–153	F. J. B.	PA	33		EtOH	69.83	70.20	4.62	4.89
2271	$-(CH_2)_4C_6H_4Br$-*p*	$C_{19}H_{15}O_3Br$	162.5–163	F. J. B.	PA	32	Needles	EtOH–C_6H_6	61.47	61.37	4.07	4.30
2244	$-(CH_2)_3C_6H_4F$-*p*	$C_{19}H_{15}O_3F$	129.8–130	E. B.	PA	54	Needles	EtOH	73.51	73.85	4.87	5.15
2373	$-(CH_2)_3C_6H_4I$-*p*	$C_{19}H_{15}O_3I$	170.5–171	E. B.	PA	45	Small needles	EtOH	54.69	54.93	3.62	3.74
2310	$-(CH_2)_3C_6H_3(CH_3)Cl$-3,4	$C_{19}H_{15}O_3Cl$	143.8–145.4	E. B.	H	41	Needles	EtOH	69.83	70.14	4.62	5.03
2346	$-(CH_2)_2C_6H_4CF_3$-*m*	$C_{19}H_{12}O_3F_3$	145–146	D. Y. C.[h]	PA	43		Lig.	65.89	66.00	3.78	4.02
2299	$-(CH_2)_3C_6H_3(CH_3)Cl$-3,4	$C_{20}H_{17}O_3Cl$	132.8–133.2	E. B.	PA	42	Needles	EtOH	70.48	70.85	5.03	5.20
2340	$-(CH_2)_5C_6H_4Cl$-*p*	$C_{21}H_{19}O_3Cl$	147–149	F. J. B.	PA	31	Small needles	Lig.–C_6H_6	71.07	71.41	5.40	5.31
2341	$-(CH_2)_5C_6H_4Br$-*p*	$C_{21}H_{19}O_3Br$	147–149	F. J. B.	PA	21	Fine needles	Lig., EtOH	63.17	63.28	4.80	4.89
2344	$-(CH_2)_9C_6H_4Cl$-*p*	$C_{25}H_{27}O_3Cl$	93–94	E. B.	PA	10		EtOH	73.07	72.84	6.62	6.66
2362	$-(CH_2)_9C_6H_4Br$-*p*	$C_{25}H_{27}O_3Br$	108.5–110.5	E. B.	PA	18	Small needles	EtOH	65.95	65.87	5.98	6.03
				Table XVII. Nitrogen-containing side chains								
1954	$-CH_2C_6H_4NO_2$-*p*	$C_{17}H_{11}O_5N$	236–237	E. B.	PA[i]	39	Needles	C_6H_6	66.08	66.44	3.53	3.64

[a] By the improved procedure of Paper XII. [b] The preparation of the intermediates for M-2309 and M-2361 is described by Huang-Minlon[3]; we are indebted to Dr. Huang for his coöperation in the preparation of a large batch of M-2309. [c] In this alkylation a by-product was isolated having the composition of the R. R. substance $[p\text{-}CH_3OC_6H_4\text{-}(CH_2)_9\text{-}]_2$; white plates, m. p. 86.5–87.2°, calcd. for $C_{32}H_{50}O_2$: C, 82.34; H, 10.80; found: C, 82.77; H, 11.16. [d] A larger sample was prepared by Dr. Huang-Minlon by alkylation; yield 55%. [e] An identical product was obtained in very low yield by alkylation of the Ag-salt according to Fieser, THIS JOURNAL, 48, 2920 (1926). [f] Initially prepared by Mary Fieser by the silver salt method; later sample prepared by F. J. B.; Hooker oxidation (26%). Acetate, m. p. 154–155°, calcd. for $C_{19}H_{13}O_4Cl$: C, 66.97; H, 3.85. Found: C, 66.87; H, 4.04. [g] In a subsequent trial of the two-step procedure described in Paper XII it was found that ring closure occurs much less readily than usual; when the heating with copper sulfate was continued for only ten minutes the intermediate ketol could be isolated in high yield as white needles from benzene–ligroin, m. p. 170–172.5°. Calcd. for $C_{19}H_{17}O_5Br$: C, 56.31; H, 4.23. Found: C, 56.90; H, 4.41. [h] Prepared by Dr. David Y. Curtin, at Harvard University. Fluorine anal.: (Tiedke). Calcd.: F, 16.46. Found: F, 15.48, 15.92. [i] An identical product was obtained by the silver salt method in very low yield along with a neutral isomer, m. p. 222–222.8° (found: C, 66.07; H, 3.49).

and 1.36 kg. (10.2 moles) of aluminum chloride was added at such a rate as to keep the reaction mixture refluxing gently (40–60 min.). It is advantageous to add the reagent rather rapidly at the beginning in order to heat the mixture and maintain the reaction complex as a mobile liquid. The mixture was refluxed for three hours, allowed to cool at 25°, and poured with stirring onto ice and 36% hydrochloric acid. The aqueous layer was siphoned off and discarded and the benzene slurry containing white solid was filtered through a sintered glass funnel. The solid was almost pure product, m. p. 116–120°. The benzene layer in the filtrate was separated and steam distilled, and the residual yellowish-white solid collected. The total crude material is suitable for Clemmensen reduction but can be purified by dissolving it in warm soda solution, clarifying this with Norit, and acidifying; the average yield of white solid, m. p. 119–121°, was 845 g. (72.5%).

γ-Aroylbutyric Acids.—The following comparison (A. G. W.) of two alternate routes to the keto acid inter-

TABLE A

INTERMEDIATES (TABLES XII–XIII)

Compound	Method	Yield, %	Notes	M. p. or b. p. °C.	Mm.	Acid chloride Yield, %	B. p. °C.	Mm.
$C_6H_5(CH_2)_4OH$[a]	$C_6H_5(CH_2)_3CO_2CH_3$, hydrog.	83		b 92–95	1.5			
$C_6H_5(CH_2)_4CO_2H$[a]	$ROH \rightarrow ROTs \rightarrow RCN \rightarrow RCO_2H$	50		m 56–57		89	120–122	4.5
$C_6H_5CO(CH_2)_4CO_2H$[b]	Fried.–Crafts; see text	62		m 70–72				
$C_6H_5(CH_2)_3CO_2H$[c]	Clemmensen–Martin	85		b 165–167	0.5	41	118–121	1.5
$C_6H_5CO(CH_2)_3CO_2H$[d]	Fried.–Crafts; see text	80		m 77–78				
$C_6H_5(CH_2)_3CO_2H$[e]	Clemmensen–Martin	95		b 209	1			
$(C_6H_5)_2CHCH_2CO_2H$ [e]	$ArCH{=}CHCO_2H$, Ar'H, $AlCl_3$	68	RCOCl, m. p. 41–42°	m 151–153			157–158	1
p-$MeC_6H_4(Ph)CHCH_2CO_2H$[f]	$ArCH{=}CHCO_2H$, Ar'H, H_2SO_4	85		m 141.6–142.4			162–164	2
$(Ph)_2CHCH_2CH_2CO_2H$[g]	From $(C_6H_5)_2CHCH_2CO_2C_2H_5$	61		m 105–107		63	178	1
$(p$-$MeC_6H_4)_2CHCH_2CO_2H$[h]	$ArCH{=}CHCO_2H$, Ar'H, H_2SO_4	62	Fd. C, 80.01; H, 7.26	m 188.6–189.8		67	187	1.5
2,4-$Me_2C_6H_3(Ph)CHCH_2CO_2H$[f]	As above with m-xylene	64		m 108–111		85	182	3.5
p-$MeC_6H_4(Ph)CH(CH_2)_2CO_2H$[g]	p-$MeC_6H_4(Ph)CHCH_2CO_2Et$	62		b 196	1.5	100	168–172	1.5
2,4-$Me_2C_6H_3CH_2CH_2CH_2CO_2H$[i]	Succinoyl., Clemm.–Martin	85	M. p. 76–76.5°	b 186–187	7			
2,5-$Me_2C_6H_3CH_2CH_2CH_2CO_2H$[i]	As above	85		b 179–180	9	78	133–135	9
3,4-$Me_2C_6H_3CH_2CH_2CH_2CO_2H$[i]	As above	70		m 55.5–56.5				
p-$EtC_6H_4COCH_2CH_2CO_2H$[j]	Succinoyl., $C_2H_2Cl_4$	80		m 102–104				
p-$EtC_6H_4CH_2CH_2CH_2CO_2H$	Clemm.–Martin	70	Crude, m. p. 68–72°	b 169–171	7			
p-i-$PrC_6H_4CH_2CH_2CH_2CO_2H$[i]	Succinoyl., $C_2H_2Cl_4$-$PhNO_2$	77	From lig.	m 46–51				
β-(β'-Tetralyl)-propionic ac.[k]	Willgerodt reaction[k]						148	1.5
γ-5-Hydrindylbutyric acid[l]	Clemm.–Martin	61		m 53–54.5				
p-$(CH_2)_3CC_6H_4(CH_2)_3CO_2H$[m]	Succinoyl., Clemm.–Martin			m 55–57.5			148–152	7
γ-(2-Me-5-i-Pr-Ph)-butyr. ac.[j]	Succinoyl., $C_2H_2Cl_4$-$C_6H_5NO_2$	Low	Used crude acid					
β-Tetralyl-$(CH_2)_2CO_2H$[n]	See text		$n^{25}D$ 1.5390	b 174–178	2	85	137–138	4
γ-1-Naphthylbutyric acid[o]	Clemm.–Mart.–Sherman redn.	80	Cryst., m 112–113	b 184–185	1	63	bath 115	0.1
γ-2-Naphthylbutyric acid[o]	Same	87	Cryst., m 101–102	b 187–189	0.2			
p-$C_6H_5C_6H_4COCH_2CH_2CO_2H$[p]	Succinoyl., $PhNO_2$	85		m 185–186				
p-$C_6H_5C_6H_4(CH_2)_3CO_2H$[p]	Clemm.–Mart.–Sherman	62	Purif. as ester	m 120–121			Not dist.	
p-Cyclohexyl-C_6H_4-$CO(CH_2)_2CO_2H$[q]	Succinoyl., $C_2H_2Cl_4$-$PhNO_2$	85	Fd. C, 73.55; H, 7.42	m 132.8–133.6				
p-Cyclohexyl-C_6H_4-$(CH_2)_3CO_2H$[q]	Clemm.–Mart.–Sberman	67	Fd. C. 78.31; H, 9.25	b 233 m 47–48.5	5			
Hydrophenanthrylbutyric acid[r]	Succinoyl., Clemm.–Martin	72		m 133–136			Not dist.	

[a] von Braun, *Ber.*, **43**, 2847 (1910); **44**, 2871 (1911). [b] Hill, THIS JOURNAL, **54**, 4105 (1932). [c] Borsche, *Ber.*, **52**, 2084 (1919). [d] Auger, *Ann. Chim.*, [6] **22**, 364 (1891). [e] Wislicenus and Eble, *Ber.*, **50**, 253 (1917). [f] Karsten, *Ber.*, **26**, 1579 (1893). [g] von Braun, Manz and Reinsch, *Ann.*, **468**, 295 (1929). [h] Cope, THIS JOURNAL, **56**, 723 (1934). [i] Barnett and Sanders, *J. Chem. Soc.*, 434 (1933). [j] Muhr, *Ber.*, **28**, 3217 (1895); present yield in CS_2: 68%. [k] Arnold, Schultz and Klug, THIS JOURNAL, **66**, 1606 (1944). [l] Fieser and Seligman, *ibid.*, **59**, 883 (1937). [m] Fieser and Price, *ibid.*, **58**, 1838 (1936). [n] Newman and Zahm, *ibid.*, **65**, 1099 (1943). [o] Martin, *ibid.*, **58**, 1438 (1936). [p] Weizmann, Bergmann and Bograchov, *Chem. Ind.*, **18**, 402 (1940); Hey and Wilkinson, *J. Chem. Soc.*, 1030 (1940). [q] Buu-Hoi, Cagniant and Mentzer, *Bull. soc. chim.*, 11, 127 (1944). [r] γ-1,2,3,4-Tetrahydro-9-phenanthrylbutyric acid.

TABLE B

ACID INTERMEDIATES (TABLES XV–XVII)

Compound	Yield, %	M. p. or b. p., °C.	Mm.
p-$CH_4OC_6H_4CO(CH_2)_2CO_2H$[a]	93	m 145–146	
p-$CH_3OC_6H_4(CH_2)_3CO_2H$[b]	65	m 59–60	
2,5-$(CH_3O)_2C_6H_3(CH_2)_3CO_2H$[c]	58	m 99–101	
p-$CH_3OC_6H_4CO(CH_2)_2CO_2H$[d]	85	m 139.5–140.5	
p-$CH_3OC_6H_4(CH_2)_4CO_2H$[d]	80	m 113–114	
p-$CH_3OC_6H_4CO(CH_2)_4CO_2H$[e]	66	m 127.8–128.6	
p-$CH_3OC_6H_4(CH_2)_6CO_2H$[e]	67	b 199–200	1
2-Dibenzfuryl-$CO(CH_2)_2CO_2H$[f]	90	m 18[illegible]	
2-Dibenzfuryl-$(CH_2)_3CO_2H$[f]	67	m 113–114.6	
p-$CH_3OC_6H_4(CH_2)_8CO_2H$[g]		m 66.7–67.7	
o-$ClC_6H_4CH_2CH_2CO_2H$[h]	87	m 95–96	
o-$BrC_6H_4CH_2CH_2CO_2H$[i]	100	m 97–98	
p-$ClC_6H_4COCH_2CH_2CO_2H$[j]	48	m 132–133	
p-$ClC_6H_4(CH_2)_3CO_2H$[j]	70	b 162–164	4
p-$BrC_6H_4COCH_2CH_2CO_2H$[k]	56	m 138–142	
p-$BrC_6H_4(CH_2)_6CO_2H$[k]	58	m 66.5–70	

[a] Fieser and Hershberg, THIS JOURNAL, **58**, 2314 (1936); Fieser and Desreux, *ibid.*, **60**, 2255 (1938). [b] Martin, Ref. 1. [c] Fieser, Gates and Kilmer, *ibid.*, **62**, 2966 (1940). [d] van den Zanden, *Chem. Abst.*, **32**, 1676 (1938); *Rec. trav. chim.*, **60**, 291 (1941); present method: anisole + glutaric anhydride in $CHCl_2CHCl_2$ + 2 moles $AlCl_3$; Clemm.–Mart.–Sherman redn. [e] Plant and Tomlinson, *J. Chem. Soc.*, 1092 (1935); present method: anisole + $EtOCO(CH_2)_4COCl$ in $CHCl_2CHCl_2$; Clemm.–Mart.–Sherman redn. [f] Gilman, Parker, Bailie and Brown, THIS JOURNAL, **61**, 2836 (1939); present method: Fried.–Crafts in C_6H_6; refl. two hours; Clemm.–Mart.–Sherman redn. [g] Procedure communicated by Dr. E. Schwenk; Fd. C, 72.86; H, 9.33. [h] Bachmann, *J. Org. Chem.*, **3**, 434 (1938); Na-Hg redn. of o-chlorocinnamic acid. [i] Method of Lingane, Swain and Fields, THIS JOURNAL, **65**, 1348 (1943). [j] Skraup and Schwameberger, *Ann.*, **462**, 135 (1938); Succinoyl. in CS_2, Clemm.–Mart.–Sherman redn. [k] Fieser and Seligman, THIS JOURNAL, **60**, 170 (1938); above procedures[j], b. 192–196° (3 mm.).

mediate for the synthesis of M-2295 indicates that the route through the half-ester acid chloride (b), although longer, is distinctly better.

(a) **Anhydride Method.**—A solution of 50 g. of tetralin and 28 g. of glutaric anhydride in 300 cc. of dry benzene was stirred mechanically and cooled to 10° and 67 g. of aluminum chloride was added in portions at such a rate

TABLE C

NEW INTERMEDIATES

Compound	Formula	Method	Notes	M. p. or b. p. °C.	Mm.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
γ-Mesitylbutyric acid	$C_{13}H_{18}O_2$	Clemm.-Martin[a]	Prod., b. p. 165° (1 mm.) 90%	90.7–91.5		75.69	76.08	8.79	9.12
β-Tetralyl-$CO(CH_2)_2CO_2H$	$C_{15}H_{18}O_3$	See text		92–93		73.25	73.10	7.36	7.79
Methyl ester	$C_{16}H_{20}O_3$	See text	B. p. 183–185° (0.5 mm.)	53–54		73.82	73.85	7.74	7.41
β-Tetralyl-$(CH_2)_4CO_2H$	$C_{16}H_{20}O_2$	Clemm.-Mart.-Sher.	80% b. p. 192° (1 mm.)	57–58.5		77.54	77.76	8.67	8.84
Chloride			B. p. 180° (2 mm.)						
p-$PhCH_2C_6H_4CO(CH_2)_2$-CO_2H[b]	$C_{17}H_{16}O_3$	Succ., $C_6H_6NO_2$ 0°	Cryst. prod., 53%	126.5–127.3		76.10	76.37	6.01	6.25
p-$PhCH_2C_6H_4(CH_2)_2CO_2H$	$C_{17}H_{18}O_2$	Clemm.-Mart.-Sher.	71% prod. b. p. 242° (4 mm.)	99.3–100.3		80.28	80.05	7.13	7.20
p-$C_6H_5OC_6H_4CO(CH_2)_4CO_2H$	$C_{18}H_{18}O_4$	RCOCl, $2AlCl_3$, C_6H_6	M. p. 98–105°, 44%	106.4–107.3		72.47	72.85	6.08	6.24
p-$C_6H_5OC_6H_4(CH_2)_5CO_2H$		Clemm.-Mart.-Sher.	B. p. 241–242° (1 mm.), 62%	m 24.5–26					
Amide	$C_{18}H_{21}O_2N$			m 103.5–104.5		76.39	76.51	7.47	7.09
p-$C_6H_5OC_6H_4CO(CH_2)_8CO_2H$	$C_{22}H_{28}O_4$	RCOCl, $2AlCl_3$, C_6H_6	Insol. Na salt 68%	m 92.3–93.3		74.55	74.61	7.40	7.50
p-$C_6H_5OC_6H_4(CH_2)_3CO_2H$	$C_{22}H_{28}O_3$	Clemm.-Mart.-Sher.	81%, m. p. 48–50	m 54.5–55.5		77.61	77.93	8.29	8.45
p-$FC_6H_4COCH_2CH_2CO_2H$[c]	$C_{10}H_9O_3F$	Succ. in CS_2	M. p. 101–102°, 30%	m 102.2–102.7		61.22	61.22	4.62	4.83
p-$FC_6H_4(CH_2)_3CO_2H$[c]	$C_{10}H_{11}O_2F$	Clemm.-Mart.-Sher.	Melts about 30°	b 161–164	4	65.92	66.24	6.09	6.22
m-$CF_3C_6H_4Br$		64%[d]		b 44–48	10				
m-$CF_3C_6H_4CH_2CH_2OH$	$C_9H_9OF_3$	ArBr + C_4H_9Li; + $(CH_2)_2O$	77%; $n^{20}D$ 1.4629	b 102	12	56.83	56.42	4.77	5.01
m-$CF_3C_6H_4CH_2CH_2Cl$	$C_9H_8ClF_3$	$SOCl_2$, $C_6H_5N(CH_3)_2$	90%; $n^{20}D$ 1.4652	b 83	12	51.82	51.93	3.87	4.05
m-$CF_3C_6H_4CH_2CH_2CO_2H$	$C_{10}H_9O_2F_3$	RMgCl + Dry Ice	60%; $n^{20}D$ 1.4678	b 149	11	55.05	55.30	4.15	4.44
Chloride	$C_{10}H_8OClF_3$	$SOCl_2$	75%; $n^{20}D$ 1.4711	b 110	10	50.76	50.82	3.41	3.60
Amide	$C_9H_{10}ONF_3$		From lig.	m 61–61.5		52.70	52.51	4.91	4.73
3,4-$MeClC_6H_3CO(CH_2)_2$-CO_2H[e]	$C_{11}H_{11}O_3Cl$	Succ. in CS_2	60% m. p. 117–118°	m 117.3–118.1		58.29	58.32	4.89	4.83
3,4-$MeClC_6H_3(CH_2)_3CO_2H$	$C_{11}H_{13}O_2Cl$	Clemm.-Mart.	86% b. p. 191–192° (5 mm.)	m 67–68.2		62.12	62.67	6.16	6.38
p-$ClC_6H_4CO(CH_2)_4CO_2C_2H_5$	$C_{14}H_{17}O_3Cl$	$C_2H_5OCO(CH_2)_4COCl$	Plates from lig. Acid,[f] m. p. 128 (91%)	m 63–63.8		62.57	63.08	6.48	6.57
p-$ClC_6H_4(CH_2)_5CO_2H$	$C_{12}H_{15}O_2Cl$	Clemm.-Mart.-Sher.	62%, b. p. 184–186° (1 mm.)	m 43–45.5		63.63	63.65	6.67	6.21
p-$BrC_6H_4CO(CH_2)_4CO_2C_2H_5$	$C_{14}H_{17}O_3Br$	$C_2H_5OCO(CH_2)_4COCl$	From pet. ether	m 66–66.9		53.69	53.70	5.47	5.58
p-$BrC_6H_4CO(CH_2)_4CO_2H$	$C_{12}H_{13}O_3Br$	Ester + alc. NaOH	70% of acid m 142	m 141.9–142.4		50.56	50.97	4.60	4.67
p-$BrC_6H_4(CH_2)_5CO_2H$	$C_{12}H_{15}O_2Br$	Clemm.-Mart.-Sher.	68% b. p. 203–205° (1 mm.)	m 50.5–51.4		53.17	53.57	5.58	5.47
p-$ClC_6H_4CO(CH_2)_8CO_2H$	$C_{18}H_{21}O_3Cl$	C_6H_5Cl + C_2H_5OCO-$(CH_2)_8COCl$ + 2 moles $AlCl_3$ in CS_2	46.5%, see text	m 98.5–100.8		64.75	64.62	7.13	7.35
p-$ClC_6H_4(CH_2)_9CO_2H$	$C_{16}H_{23}O_2Cl$	C.-M.-Sher. (86%)	Isolat. by cryst.	m 54.5–57.5		67.95	68.24	8.20	8.39
p-$BrC_6H_4CO(CH_2)_8CO_2H$	$C_{16}H_{21}O_3Br$	F. C. in CS_2 (47%)	Plates from benzene	m 115.5–117.5		56.31	56.52	6.20	6.27
p-$BrC_6H_4(CH_2)_9CO_2H$		C.-M.-Sher. (67%)	Isolat. by cryst.	m 63–66		58.72	58.82	7.08	7.13

[a] Of β-mesitoylpropionic acid, Meyer, *Ber.*, **28**, 1269 (1895). By adding aluminum chloride to mesitylene and succinic anhydride in tetrachloroethane and allowing the solution to stand for two hours at 25°, crude acid satisfactory for reduction was obtained in 91% yield. [b] Cook, Robinson and Roe, *J. Chem. Soc.*, 266 (1939). [c] Prepared by Ruth Alice Davis. [d] Booth, Elsey and Burchfield, THIS JOURNAL, **57**, 2066 (1935). [e] Oxidation by alkaline potassium permanganate to an acid, m. p. 207–208.4° (from water); 4-chloro-3-methylbenzoic acid melts at 209–210°. [f] Skraup and Guggenheimer, *Ber.*, **58**, 2496 (1925), report the m. p. 130°; our acid, recrystallized from benzene–ligroin, melted at 132–133°.

that the temperature remained below 15°. The mixture was stirred for eight hours longer and then allowed to stand overnight at room temperature. The mixture was decomposed with ice and acid in the usual way, steam distilled, and the soda-soluble fraction (clarified with Norit and filtered through Supercel) was crystallized from benzene–ligroin. Three crystallizations afforded 26.0 g. (43%) of pure γ-2-tetraloylbutyric acid (Table C) in the form of colorless needles, m. p. 92–93°.

(b) **Ester-Acid Chloride Method.**—A solution of 132 g. of tetralin in 1 l. of nitrobenzene was stirred mechanically in an ice-bath and 268 g. of aluminum chloride was added. A solution of 165 g. of γ-carbomethoxybutyryl chloride in 300 cc. of nitrobenzene was then added slowly from a dropping funnel with maintenance of a temperature of 0–5°. The dark solution was stirred in the ice-bath for four hours and let stand overnight at room temperature. The solution was then shaken with ice and hydrochloric acid in a separatory funnel and the lower organic layer drawn off. The aqueous layer was extracted once with ether and the combined organic extract was evaporated in vacuum and the residue refluxed for one-half hour with methanol and sulfuric acid to esterify a small amount of free acid present. Distillation of the neutral ester fraction then afforded 184 g. (71%) of satisfactory methyl γ-2-tetraloylbutyrate (b. p. 183–185° (0.5 mm.), m. p. 53–54°).

Δ-Aroylvaleric Acids.—**Δ-Benzoylvaleric acid** was prepared both from adipic polyanhydride[6] (C. H., 62%) and from ethyl hydrogen adipyl chloride[7] (F. J. B., 55%); although the yield by the first method was somewhat higher, the crude product was yellow and of inferior character. The second method was preferred for the preparation of substituted acids of the series.

(6) Hill, THIS JOURNAL, **54**, 4105 (1934).

(7) Raper and Wayne, *Biochem. J.*, **22**, 188 (1928).

TABLE D

OTHER INTERMEDIATES

Acid	Formula	Method	Yield, %	M. p., °C.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
β-*p*-Iodobenzoylpropionic	$C_{10}H_9O_3I$	Succ. CS_2, cryst. EtOH	14	180.5–181.8	39.49	39.78	2.98	3.26
γ-*p*-Iodophenylbutyric[a]	$C_{10}H_{11}O_2I$	Clemm. redn., 6 hr. 90°	42	89–90.5	41.40	41.83	3.82	3.99
β-(2,5-Diethoxybenzoyl)-propionic	$C_{14}H_{18}O_5$	Succ. $C_6H_5NO_2$–$CHCl_2CHCl_2$	60	147.4–148.6	63.14	63.20	6.81	7.08
γ-(2,5-Diethoxyphenyl)-butyric	$C_{14}H_{20}O_4$	Modif. Wolff–Kishner[3]	70	117.8–118.6	66.64	66.75	7.99	8.30
δ-2-Thenoylvaleric[b]	$C_{10}H_{12}O_3S$	C_4H_4S + RCOCl to CS_2–$AlCl_3$	38	78.7–79.7	56.58	56.74	5.70	5.90
ε-2-Thienylcaproic	$C_{10}H_{14}O_2S$	Clemm. redn. 25°, 30 hr.	64	41.4–42.8	60.61	60.72	7.12	7.18
ω-2-Thenoylnonanoic[b]	$C_{14}H_{20}O_3S$	C_4H_4S + RCOCl	26	60–61.5	62.65	62.50	7.51	7.52
γ-*p*-Nitrophenylbutyric[c]	$C_{10}H_{11}O_4N$	See note	25	91.5–92.5	57.41	57.20	5.31	4.97
β-*p*-*t*-Amylbenzoylpropionic	$C_{15}H_{20}O_3$	Succinoylat. in CS_2		101–102	72.55	72.79	8.12	8.33
10-Keto-10-(β-ar-tetralyl)-capric[d]	$C_{20}H_{28}O$	Sebac. polyanhyd. + $C_{10}H_{12}$	Low	57–60	75.91	75.74	8.91	9.03

[a] The melting point corresponds to that of the acid prepared by Plati, Strain and Warren, THIS JOURNAL, **65**, 1273 (1943), by iodination of phenylbutyric acid. [b] Prepared by a different procedure by Billman and Travis, *Chem. Abst.*, **40**, 1826 (1946); present procedure: addition of thiophene + $C_2H_5OCO(CH_2)_8COCl$ in $CHCl_2CHCl_2$ to $C_6H_5NO_2$–$AlCl_3$ at 0°; steam distillation from sodium hydroxide. [c] Van der Scheer, THIS JOURNAL, **56**, 744 (1934). Present procedure: 70 cc. nitric acid (1.42) + 30 cc. 96% sulfuric acid added slowly at 38° to 43 g. $C_6H_5(CH_2)_3CO_2H$ + 70 cc. 96% sulfuric acid + 150 cc. HOAc. [d] In $C_6H_5NO_2$–$AlCl_3$ at 25°; attempted peroxide alkylation with this keto acid was unsuccessful (A. G. W.).

Ethyl hydrogen adipyl chloride was obtained[8] in 82.5% yield as a liquid, b. p. 92–93° (2 mm.), from 118.2 g. of ethyl hydrogen adipate and 62 cc. of thionyl chloride, refluxed in benzene for two hours; the solvent was evaporated at the water pump, and three fresh portions of dry benzene were added and evaporated. δ-*p*-Bromobenzoylvaleric acid (F. J. B.) was prepared by gently refluxing a mixture of 58 g. (0.3 mole) of ethyl adipyl chloride, 63 g. (0.4 mole) of bromobenzene, 100 cc. of carbon bisulfide, and 80 g. (0.6 mole) of aluminum chloride for sixteen hours. After the usual treatment with ice and acid the intermediate ester was collected by ether extraction and hydrolyzed to the acid, which was obtained in a satisfactory condition on one crystallization from benzene in 70% yield (see Table C for properties). When the reaction was conducted in tetrachloroethane at 0°, followed by a brief terminal period of heating, the yield was only 56% and the acid was much less pure. However, application of the same procedure to a Friedel and Crafts reaction with chlorobenzene (in $CHCl_2CHCl_2$, iced) afforded δ-*p*-chlorobenzoylvaleric acid in 91% yield; the yield dropped to 77% when the reaction mixture was initially heated at 40–50°.

δ-*p*-Phenoxybenzoylvaleric acid (F. J. B.) was prepared in much the same way except that benzene was used as solvent. The aluminum chloride was added in small portions with shaking to a cooled solution of the other components and each time the reaction was allowed to subside before a fresh portion was added. When the addition was complete the mixture was allowed to come to room temperature in the course of about one hour and then heated on the steam-bath for fifteen minutes. The crude ester obtained by the usual processing was a reddish oil and was hydrolyzed without purification; the crude acid was a cream-colored solid and was suitable for reduction after one crystallization from benzene–ligroin (yield 44%).

In all of the reactions of this and other half-ester acid chlorides it is essential that two moles of aluminum chloride be employed per mole of chloride.

ω-Aroylnonanoic Acids (E. B.).—The best yield of ω-benzoylnonanoic acid resulted from the use of ethyl sebacyl chloride prepared with thionyl chloride in benzene, as above. A solution of the chloride from 125 g. of half-ester in 200 cc. of thiophene-free benzene was added in the course of two hours to a stirred suspension of 150 g. of aluminum chloride in 1 l. of benzene and the mixture was allowed to warm up and then to stand overnight. After the usual processing, hydrolysis, and one crystallization from ligroin, satisfactory acid, m. p. 77–78°, was obtained in yield of 114 g. (80%).

ω-*p*-Chlorobenzoylnonanoic acid was first prepared by a similar procedure but with one equivalent of chlorobenzene in tetrachloroethane, but the yields were low and irregular (0.1 mole runs): 9.0, 5.4, 5.1, 14.3, 25.7% (when only one mole of aluminum chloride was used no product could be isolated). A more satisfactory procedure was found in the use of carbon bisulfide as solvent and by isolation of the acid as the sodium salt. Aluminum chloride (64 g.) was added in portions to a cooled solution of 35 g. of chlorobenzene and 52 g. of ethyl sebacyl chloride in 150 cc. of carbon bisulfide and the mixture was refluxed overnight and then processed with ice and acid and steam distilled. The solid product, which was the free acid rather than the ester, was dissolved in warm dilute alkali and the solution was clarified with Norit, and treated with 50 g. of sodium chloride (volume about 500 cc.). The sodium salt that separated was collected, washed with ice water and with a little ether, dissolved in water and salted out as before. After a third precipitation from 300 cc. of water with 25 g. of sodium chloride the pure white salt was suspended in water and acidified and the acid collected, dried, and crystallized once from benzene and a little ligroin; yield 28.8 g. (46.5%). The same procedure was found applicable to the preparation of **ω-*p*-bromobenzoylnonanoic acid** and much better than reaction in tetrachloroethane. The crude reaction product separated as an oily precipitate and was extracted with ether and recovered from the clarified solution prior to purification through the sodium salt (the yield dropped to 21% when the ether extraction was omitted).

Benzene proved to be a satisfactory solvent for the preparation of **ω-*p*-phenoxybenzoylnonanoic acid**, but it was found advantageous to change the above procedure as follows: A solution of 17 g. of the acid chloride and 14 g. of diphenyl ether in 25 cc. of benzene was added in several portions, without cooling or stirring, to a suspension of 21 g. of aluminum chloride in 100 cc. of benzene. After the initial reaction had subsided the mixture was refluxed for thirty minutes and processed further as above. The reaction product was the free acid and was purified through the sodium salt, which is much less soluble than the salts of the halo-acids. The yield of acid once crystal-

(8) Bishop, "Organic Syntheses," **25**, 71 (1945).

lized from benzene–ligroin was 68%. Yields of 51 and 48% resulted when the acid chloride was added to a mixture of the other reagents.

Clemmensen Reduction.—In the early stages of the work Clemmensen reductions were conducted by Martin's procedure,[1] usually with the use of added acetic acid. The improvements introduced by Sherman[2] were found to be highly advantageous, and his modified procedure was followed in all subsequent work. The zinc, prior to amalgamation, is melted in a casserole and poured into a large volume of water. The reduction is carried out according to Martin except that the reaction flask, heated most conveniently with a Glass-Col mantle, is provided with a Hershberg stirrer to effect vigorous agitation. A typical charge is: 93 g. of β-naphthoylpropionic acid, 185 cc. of sulfur-free toluene, 41 cc. of acetic acid, 140 cc. of water, 185 g. of freshly poured zinc amalgamated with 16.3 g. of mercuric chloride, 322 cc. of 36% hydrochloric acid (added cautiously). Fresh portions of 36% acid (70 cc.) are added at the end of the first, second and third hour. The observations that we have made tend to show that the Sherman improvements reduce the reaction time from thirty-six to forty-eight hours to four to six hours, without any material change in the yield.

Other Acids.—A few additional acids that are either new or were prepared by improved methods are listed in Table D. In the two Friedel–Crafts acylations of thiophene it was found advantageous to slowly add a solution of thiophene and the half-ester acid chloride to a suspension of aluminum chloride. In the Clemmensen reduction of δ-2-thenoylvaleric acid at room temperature it was noted that the solid keto acid turned to an oil during the first half hour of stirring. In one attempted alkylation with ε-2-thienylcaproic acid the peroxide was obtained in 15% yield but no alkylation product could be isolated and the acid was recovered unchanged.

Hooker Oxidation (E. B., F. J. B.).—Several of the oxidations reported were on quinones whose sodium salts are very sparingly soluble in water, and the reaction consequently was conducted in a dioxane–water mixture. The quinone was dissolved in a suitable amount of cold dioxane and the solution poured into water (200–300 cc. per gram quinone) containing 5–10 pellets of sodium hydroxide. Oxidation was done with 211 g. of permanganate + 5 % excess per mole of quinone and 4–5 g. of sodium hydroxide per gram of quinone.

Summary

Eighty new 2-hydroxy-1,4-naphthoquinones substituted in the 3-position with aralkyl and substituted aralkyl groups are described. In the course of the preparation of the acids required for peroxide alkylation, comparative studies were made of various modifications of the Friedel–Crafts condensation of mono- and bicylic benzenoid derivatives with the anhydrides and ester–acid chlorides of the available dibasic acids, and of the efficiency and generality of the reduction of the keto acids by the Clemmensen and Wolff–Kishner methods as improved by Martin and by Sherman, in the first instance, and by Whitmore, Soffer, and Huang-Minlon, in the second.

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Naphthoquinone Antimalarials. IV–XI. Synthesis. IX. Aryl Derivatives

The peroxide reaction is of very limited application in the arylation of 2-hydroxy-1,4-naphthoquinone. The diaroyl peroxides are more stable than the aliphatic peroxides and the reaction is best conducted at 105–115°; under these conditions 3-aryl derivatives were obtained from 2-methyl-1,4-naphthoquinone in six of ten cases tried. However, attempted arylation of hydroxynaphthoquinone was successful only with the peroxides from *m*- and *p*-nitro and *p*-bromobenzoic acid (Table XIV) and the reaction failed with the peroxides of *m*- and *p*-methyl- and *o*-bromobenzoic acid and of α- and β-naphthoic acid. In both the successful and unsuccessful instances, a considerable amount of high-melting, sparingly soluble by-product was formed.

The method of decomposing a diazonium salt in the presence of the hydroxyquinone has proved of more service in extending this series but it is at best a poor synthetic reaction. Neunhoeffer and Weise[1] conducted the reaction in an alkaline medium, and this procedure, designated "Diaz.-alk." in the Table, has been studied particularly at the Bryn Mawr Laboratory (E. Berliner and F. J. Bondhus). An alternate procedure developed by Mao-i Wu consists in adding a solution of the diazotized amine to a solution at 40–60° of the hydroxyquinone in acetic acid containing suspended copper powder ("Diaz.-Cu, 40°"), and a variation of the procedure is to conduct the reaction in an acetic acid solution of cupric chloride at the boiling point (M. Fields). The present results do not permit any general conclusion regarding the relative merits of the three procedures. There is considerable variation from compound to compound, both in the manner in which the arylation itself proceeds and in the ease of recovery of the product. In most cases the aryl-substituted quinone is isolated in a pure condition only with considerable difficulty and with considerable loss of material. Except for the yields given in parentheses, which indicate approximate results in first trials conducted on a very small scale, the yields recorded refer to fully purified products and are usually averages of several experiments. The yield fell off sharply whenever the quantity of amine taken was over 0.1 mole, and hence material sufficient for assay had to be made in several small batches. Several of the compounds listed were not submitted for assay.

(1) Neunhoeffer and Weise, *Ber.*, **71**, 2703 (1938).

Experimental

Arylation of a Diazonium Salt and Copper Powder in Acetic Acid Solution.—The general procedure is illustrated by the following description of the preparation of M-1743, 2-hydroxy-3-*p*-sulfonamidophenyl-1,4-naphtho-

TABLE XIV

2-HYDROXY-3-ARYL-1,4-NAPHTHOQUINONES

M-	Aryl group —C_6H_4	Formula	M. p., °C.	Prepared by	Method	Yield, %	Notes	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
2313	*o*-Chloro	$C_{16}H_9O_3Cl$	194–195.5	M. W.	Diaz.–Cu, 40°	Low					
				E. B.	Diaz.–Alk.	Low	Needles	67.50	67.67	3.18	3.12
1932	*m*-Chloro	$C_{16}H_9O_3Cl$	203–204	M. W.	Diaz.–Cu, 40°	(20)		67.50	67.86	3.18	3.38
1938	*p*-Chloro	$C_{16}H_9O_3Cl$		M. W.	Diaz.–Cu, 40°	30	Needles	67.50	67.53	3.18	3.55
			187.4–188	E. B.[a]	Diaz.–Alk.	22	EtOH–C_6H_6				
1937	*o*-Bromo	$C_{16}H_9O_3Br$	196–197	M. W.	Diaz.–Cu, 40°	(20)		58.38	58.26	2.76	2.99
1006	*m*-Bromo	$C_{16}H_9O_3Br$	143–145	M. W.	Diaz.–Cu, 40°	(20)		58.38	58.37	2.76	3.00
1935	*p*-Bromo	$C_{16}H_9O_3Br$	193.8–194.8	M. W., M. F.	PA, Diaz.–Cu	18, 21	Needles	58.38	58.41	2.76	3.23
				M. W.	Diaz.–Cu, 40°	31	EtOH–C_6H_6				
				E. B.[b]	Diaz.–Alk.	25					
2212	*p*-Iodo	$C_{16}H_9O_3I$	177.6–179.6	M. F.	Diaz.–Cu, b. p.	11	Needles	51.08	51.32	2.67	2.64
2217	*p*-Fluoro	$C_{16}H_9O_3F$	186.5–187	M. F.	Diaz.–Cu, b. p.	18	C_6H_6 (repeated)	71.40	72.02	3.75	3.63
1973	2,4-Dichloro	$C_{16}H_8O_3Cl_2$	223–224	M. W.	Diaz.–Cu, 40°	(20)		60.21	60.30	2.53	2.82
1966	2,5-Dichloro	$C_{16}H_8O_3Cl_2$	211–212	M. W.	Diaz.–Cu, 40°	(20)		60.21	60.35	2.53	2.88
2288	*p*-Methoxy	$C_{17}H_{12}O_4$	174–175	M. W.	Diaz.–Cu, 40°	Low		72.85	72.75	4.32	4.33
			174.9–176.9	F. J. B.	Diaz.–alk.	6	Needles	72.85	73.31	4.32	4.52
2298	*p*-Ethoxy	$C_{18}H_{14}O_4$	207–208	F. J. B.	Diaz.–alk.	9	Needles	73.46	73.77	4.80	5.11
1743	*p*-SO_2NH_2	$C_{16}H_{11}O_5SN$	288	M. W.	Diaz.–alk.	10	Acetone-lig.	58.35	58.05	3.37	3.57
			289–290	M. W.	Diaz.–Cu, 40°	27	Acetone-lig.				
	Acetate	$C_{18}H_{13}O_6NS$	203–204		Ac_2O–NaOAc		From EtOH	58.22[d]	58.12	3.53	3.80
	Hydroquinone triacetate	$C_{22}H_{19}O_8NS$	239–240		Red. acetylat.		From EtOH	57.76	57.80	4.19	4.20
1925	*p*-SO_2NH-2-Pyridyl	$C_{21}H_{14}O_5N_2S$	242–243	M. W.	Diaz.–Cu, 40°	(20)		62.06	62.30	3.47	3.38
	Acetate	$C_{25}H_{18}O_6N_2S$	216–217		Ac_2O–NaOAc			61.60	61.78	3.60	3.71
1919	*p*-$SO_2NHC(NH_2)$=NH	$C_{17}H_{13}O_5N_3S$	271–272	M. W.	Diaz.–Cu, 40°	(20)		54.98	54.54	3.53	3.64
	Acetate	$C_{19}H_{16}O_6N_3S$	225–226		Ac_2O–NaOAc			55.20	54.96	3.66	4.02
1007	*p*-SO_2NH-2-Thiazolyl	$C_{19}H_{12}O_5N_3S_2$	274–275	M. W.	Diaz.–Cu, 40°	(20)		55.33	55.46	2.93	3.27
	Acetate	$C_{21}H_{14}O_6N_3S_2$	219–220		Ac_2O–NaOAc			55.50	55.64	3.11	3.31
1008	*p*-SO_2NH-2-Sulfadiazinyl	$C_{20}H_{12}O_5N_4S$	267–269	M. W.	Diaz.–Cu, 40°	(20)		58.96	58.57	3.22	3.50
2300	*m*-CH_3	$C_{17}H_{12}O_3$	140.5–141.5	E. B.[e]		10	EtOH: plates	77.26	77.18	4.57	4.70
2225	2-Methyl-4-chloro	$C_{17}H_{11}O_3Cl$	210–211	M. F.	Diaz.–Cu, b. p.	7	Needles	68.35	68.40	3.71	3.83
1009	2-Methyl-4-bromo	$C_{17}H_{11}O_3Br$	223.5–224.5	M. F.	Diaz.–Cu, b. p.	21	From C_6H_6	59.54	59.36	3.23	3.25
2307	2,4-$(CH_3)_2$	$C_{18}H_{14}O_3$	178.5–179.5	F. J. B.	Diaz.–alk.	11	Needles	77.68	77.60	5.07	5.30
1010	*p*-CH_3CO	$C_{18}H_{12}O_4$	214–215	M. W.	Diaz.–Cu, 40°	(20)		73.96	74.21	4.17	4.07
1011	*m*-NO_2	$C_{16}H_9O_5N$	272–272.5	M. W., E. B.	PA	Low	From HOAc	65.08	64.96	3.07	3.10
1012	*p*-NO_2	$C_{16}H_9O_5N$	280–283	M. W., E. B.	PA	Low	HOAc: needl.	65.08	65.06	3.07	3.17
2278	-α-Naphtbyl	$C_{20}H_{12}O_3$	153–154	E. B.	Diaz.–alk.	10	Lig.: needl.	79.98	80.27	4.03	4.34
1958	-*p*-Xenyl	$C_{28}H_{14}O_3$	220–221	M. W., M. F.	Diaz.–Cu, 40°	4	C_6H_6: needl.	80.97	80.70	4.32	4.12
				M. F.	Diaz.–Cu, b. p.	20					

[a] With Miss Bondhus and Mrs. Harvey Satenstein. [b] With Miss Bondhus. [c] Neunhoeffer and Weise, *Ber.*, **71**, 2703 (1938), report the m. p. 127°. [d] Calcd.: N, 3.77. Found: N, 3.79. [e] With Miss Margaret Bloomfield.

quinone; the method gave a better yield and a purer product than the alkaline method. A solution of 5 g. of sulfanilamide in 7 cc. of 36% hydrochloric acid and 30 cc. of water was diazotized at 0–5° with 2.6 g. of sodium nitrite in 15 cc. of water and the solution was added in portions with stirring to a solution at 40–60° of 5 g. of hydroxynaphthoquinone in 150 cc. of acetic acid to which 2 g. of copper powder had been added. Vigorous gas evolution occurred each time more solution was added and a light yellow solid separated. The temperature was kept at 40–60° during the addition, which was completed in ten to fifteen minutes. The mixture was then heated on the steam-bath, cooled, and the precipitated solid collected, washed with a little acetone, and then extracted with boiling acetone. The filtered solution on cooling deposited 1.5–3.5 g. of fine yellow crystals, m. p. 289–290°.

In some other instances the acetic acid solution at first deposited only a little resinous material; this was removed by filtration and the solution let stand for several hours and filtered from a further lot of resin. The process was repeated several more times until finally crystalline and nearly pure product separated. In the case of the halogenated derivatives the reaction mixture was diluted with water and the very crude precipitated product was stirred well with a very small amount of 10% alcoholic alkali, which precipitates the salt of the starting material but leaves that of the aryl derivative in solution; the filtered solution was acidified and diluted and the product collected. Sometimes reprecipitation from a solution in 1% aqueous alkali effects further purification.

This procedure failed to give any product when applied to aniline, *o*-toluidine, α-naphthylamine, 4-bromo-1-naphthylamine, 2-methyl-5-isopropylaniline, and *p*-*t*-amylaniline.

Reaction in HOAc–$CuCl_2$ at a Higher Temperature.—As applied to the preparation of 2-hydroxy-3-*p*-xenyl-1,4-naphthoquinone, the above procedure gave a much better yield when the reaction was conducted in boiling acetic acid rather than at 45°. The modified procedure illustrated by the following example was therefore adopted in one of the three series of preparations. The diazonium salt solution from 12.1 g. of *p*-fluoroaniline was added slowly to a rapidly stirred solution of 11.1 g. of hydroxy-

TABLE A

OTHER 3-SUBSTITUTED 1,4-NAPHTHOQUINONES

3-Substituent	Formula	M. p., °C.	Method	Yield, %	Notes	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
2-Hydroxy-3-arylazo-1,4-naphthoquinones									
o-$ClC_6H_4N{=}N$- [a]	$C_{16}H_9O_3N_2Cl$	215.3–216.2	By-product	12	C_6H_6–EtOH; orange	61.45	61.40	2.90	2.87
p-$BrC_6H_4N{=}N$-	$C_{16}H_9O_3N_2Br$	231.5–232.5	In $CHCl_3$ + Cu	13	Attempted arylation	53.80	53.91	2.54	2.53
p-$NH_2SO_2C_6H_4N{=}N$-	$C_{16}H_{11}O_4N_3S$	281–283	HOAc–NaOAc [b]	73	Delib. coupling	53.78	53.82	3.10	3.03
p-$C_6H_5C_6H_4N{=}N$-	$C_{22}H_{14}O_3N_2$	248–249	Acetone-NaOAc-$CuCl_2$	53	Attempted arylation	74.40	74.67	4.25	3.94
p-$C_6H_4OC_6H_4N{=}N$-	$C_{22}H_{14}O_4N_2$	228.4–229.2	By-product	v. low	EtOH, red needles	71.35	71.36	4.79	4.47
3-Substituted 2-Methyl-1,4-naphtboquinones Prepared by the Peroxide Reaction (M. W.)									
$ClCH_2$-	$C_{12}H_9O_3Cl$	107–108		v. low		65.32	65.61	4.11	4.77
$BrCH_2$-	$C_{12}H_9O_3Br$	134–135		v. low		54.36	54.67	3.42	3.53
n-$C_{11}H_{23}$-	$C_{24}H_{36}O_3$	90.2–91		33		80.93	81.17	9.26	9.04
n-$C_{13}H_{27}$-	$C_{24}H_{34}O_2$	94.6–95.2		55		81.31	81.50	9.67	9.56
m-$CH_3C_6H_4$	$C_{18}H_{14}O_2$	118–120		31		82.42	82.63	5.38	5.46
p-$CH_3C_6H_4$	$C_{18}H_{14}O_2$	154.5–156		31		82.42	82.66	5.38	5.33
m-BrC_6H_4-	$C_{17}H_{11}O_3Br$	158.5–160		16		62.41	62.56	3.39	3.37
p-BrC_6H_4-	$C_{17}H_{11}O_3Br$	174.5–175.6		21		62.41	62.54	3.39	3.60
m-$NO_2C_6H_4$-	$C_{17}H_{11}O_4N$	224.5–226.5		34		69.62	69.70	3.78	3.59
p-$NO_2C_6H_4$-	$C_{17}H_{11}O_4N$	183–184		68		69.62	69.70	3.78	3.83

[a] Prepared by Mrs. Harvey Satenstein. [b] Coupling procedure of Kehrmann and Goldenberg, *Ber.*, **30**, 2125 (1897).

naphthoquinone in 500 cc. of boiling acetic acid containing 2.5 g. of cupric chloride dihydrate and the solution was kept at the boiling point and stirred for one-half hour after the addition was complete. The solution was then concentrated at reduced pressure to about 50 cc. and the yellow solid that separated was purified by precipitation from a filtered solution in hot 1% alkali and crystallized from benzene. This gave 3.25 g. (19%) of M-2217: 2-hydroxy-3-*p*-fluorophenyl-1,4-naphthoquinone, m. p. 183.5–186°; and three more recrystallizations gave 3.0 g. of constant-melting material of sharp m. p. (repeated further crystallization did not change the m. p. or analysis).

Arylation with a Diazonium Salt in Alkali.—In the procedure most generally followed, 0.1 mole of the amine was brought into solution by heating it with 25–30 cc. (0.3–0.36 mole) of 36% hydrochloric acid and 100–400 cc. of water (depending on the solubility), and the solution if colored or not clear was boiled with Norit and filtered. Diazotization was done at 0–5° with 7.2 g. (0.105 mole) of sodium nitrite in 50 cc. of water and the solution was added slowly to a stirred solution at 40–45° of 9 g. (0.005 mole) of hydroxynaphthoquinone in 700 cc. of 5% potassium hydroxide (if more hydrochloric acid is used to dissolve the amine the amount of alkali is increased proportionately); small amounts of ether were sometimes added to disperse the foam. The mixture was stirred at 45° for about twenty minutes, filtered, acidified to *p*H 6, and the crude precipitated material was crystallized as required.

In one arylation experiment with diazotized *o*-chloroaniline the amount of hydrochloric acid was increased from 30 cc., with which a satisfactory result had been obtained, to 40 cc.; the only product that could be isolated proved to be the arylazo derivative (for properties, see Table A). In an attempted arylation with the diazonium salt from *p*-aminodiphenyl the azo derivative was the only product isolated. 2-Hydroxy-3-β-naphthyl-1,4-naphthoquinone[1] was obtained by the above procedure in 17–22% yield in runs of 10–14 g.; a run with 20 g. gave much less pure product in 15% yield. When the amount of hydrochloric acid was increased beyond 30 cc. per 0.1 mole the solution did not require filtering and the product was of superior quality but the yield was only 9%. The *o*-tolyl derivative[1] proved to be very difficult to obtain in crystalline form. Two or three unsuccessful attempts were made to effect arylation with the following amines: *p*-arsanilic acid, 2-aminodibenzfuran, methyl 2-aminobenzoate, 1-amino-2-methylanthraquinone, 3-aminoacenaphthene, *o*-anisidine, and *p*-aminoazobenzene. The 2-fluoryl derivative was obtained in extremely low yield as red needles, m. p. 240–242°, but the carbon content was 0.6% low.

Other Substituted Quinones.—The arylazo derivatives isolated as by-products or on deliberate coupling of the components in aqueous sodium acetate–acetic acid solution are listed in Table A.

The second group of compounds listed in Table A are 3-alkyl or aryl derivatives of 2-methyl-1,4-naphthoquinone isolated in a further exploration of the peroxide reaction. The peroxides of chloroacetic[2] and bromoacetic acid are too unstable to permit determination of the yield by titration, but nevertheless the halomethylation of methylnaphthoquinone was accomplished with both reagents, if in very low yield. Higher aliphatic diacyl peroxides are about as effective in the alkylation of the methylnaphthoquinone as they are in the alkylation of the hydroxy compound. The six peroxide arylations of methylnaphthoquinone reported were conducted best at 105–115°; and the reactions proceeded about as satisfactorily as the typical alkylations of the hydroxy quinone. Attempted arylations with the peroxides of benzoic, α-naphthoic, and β-naphthoic acid were unsuccessful.

Summary

Arylation of hydroxynaphthoquinone by the peroxide method usually proceeds in low yield or not at all. The method of decomposing a diazonium salt in the presence of a quinone acceptor is more generally applicable and was employed for the synthesis of a number of new compounds, but the yields are very low.

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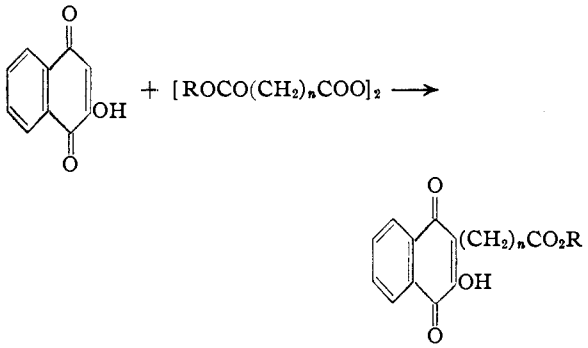
(2) Price, Kell and Krebs, THIS JOURNAL, **64**, 1103 (1942).

Naphthoquinone Antimalarials. IV–XI. Synthesis.

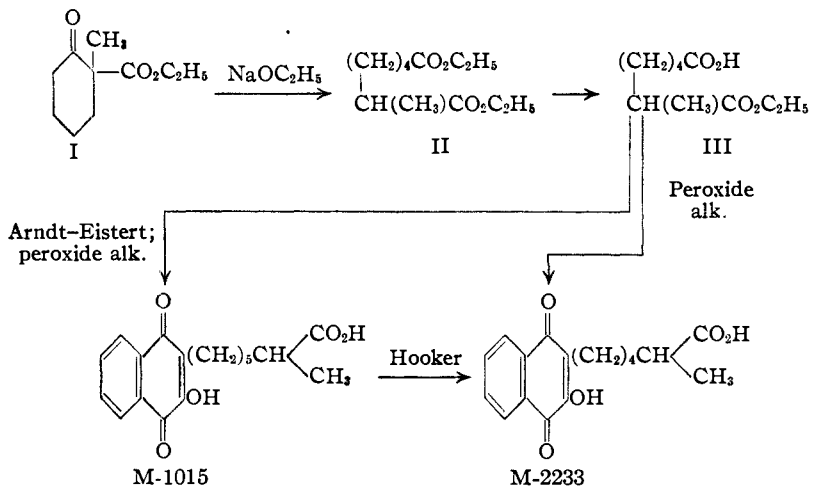
X. Miscellaneous Compounds with Oxygen, Halogen or Nitrogen in the Side Chain

The aralkyl derivatives containing O-, Hal.- and N-substituents have already been considered in Paper VIII, and the Mannich bases listed in Assay Table XVII are described in Paper XIII. The remaining quinones with substituted side chains are listed in the present Tables XV–XVII arranged in chemically related groups.

Carboxyl Derivatives.—2-Hydroxy-3-carbethoxy-1,4-naphthoquinone was prepared from 2-carbethoxy - 1,3 - dihydroxynaphthalene. The other members of the series were made by alkylation with the peroxide from the half ester or



anhydride of a dibasic acid and saponification of the resulting ester.[1] The propionic acid derivative resulting from the reaction with succinic acid half-peroxide separated initially in the form of the lactone, which was converted through the ester to the acid. Quinones with a methyl group α- to the carboxyl function, desired for comparison with metabolites of the isoalkyl series, were obtained by a synthesis starting with 2-carbethoxycyclohexanone. This was converted by methylation (I), alkoxide cleavage (II), and partial saponification to a half-ester of probable structure III that was employed for the synthesis of M-2233. The half ester III was also converted by the Arndt–Eistert reaction to the next higher homolog and this was used for peroxide alkylation to M-1015. The observation that Hooker oxidation of M-1015 gave a quinone identical with M-2233 proves that the hydrocarbon chain suffered no alteration in the reaction with diazomethane.



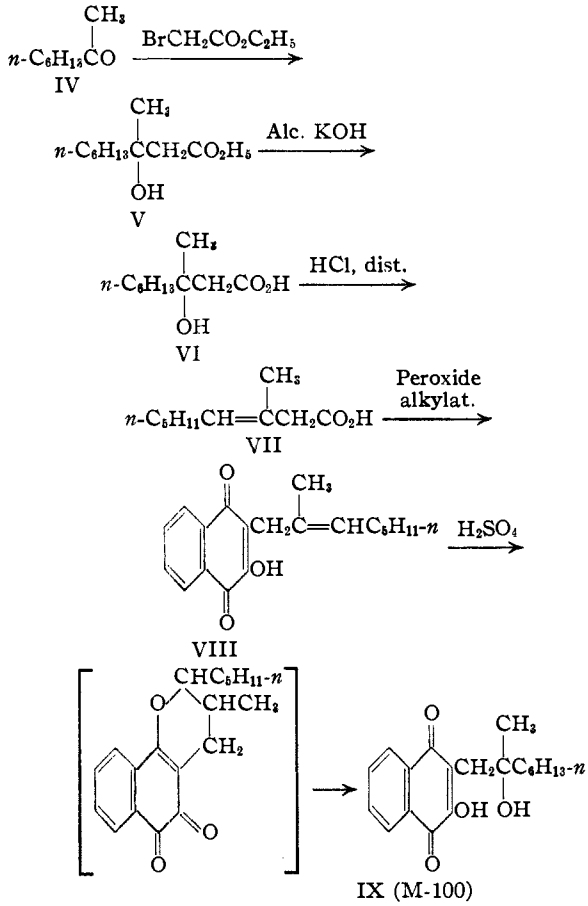
Ethers.—The two aliphatic ether derivatives M-308 and M-359 were prepared by peroxide alkylation; the reaction proceeds best when the ether linkage is distant from the carboxyl group (attempted alkylation with methoxyacetic acid has been unsuccessful).

Alcoholic Derivatives.—The first of three general synthetic methods developed was applied to the synthesis of 2-hydroxy-3-(β-hydroxy-β-methyloctyl)-1,4-naphthoquinone (M-100), the β-hydroxy derivative of M-285; at the time, this appeared to be a likely structure for the product of the metabolic degradation of M-285. Methyl *n*-hexyl ketone (IV) was converted by a Reformatsky reaction to the hydroxy ester V, and this was saponified and the acid VI dehydrated by distillation with a trace of hydrogen chloride. The product appeared, from its ability to decolorize bromine solutions and its low refractive index, to be the β,γ-unsaturated acid VII; other methods of dehydration gave products that seemed to consist wholly or partly of the bromine-inert α,β-unsaturated acid with which the peroxide alkylation of hydroxynaphthoquinone could not be accomplished. Such alkylation proceeded satisfactorily with the peroxide of the β,γ-unsaturated acid VII and gave an apparently homogeneous unsaturated quinone VIII. Under the conditions employed by Hooker for the production of β-lapachone,[2] this underwent cyclization to a neutral product that was not isolated but that on hydrolysis afforded an alcoholic derivative of the probable structure IX (M-100).

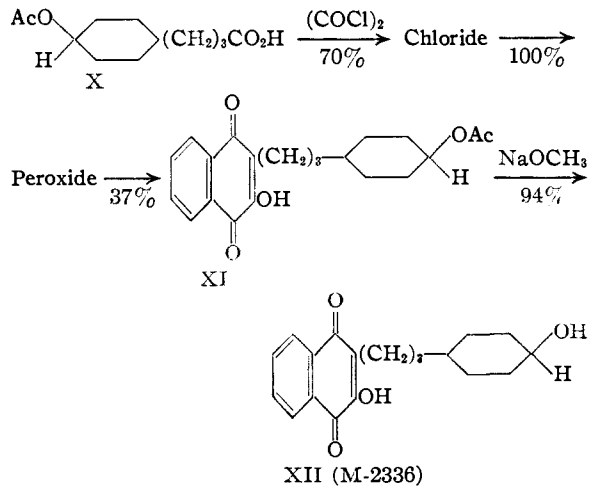
A second method was employed for the synthesis of a 4′-hydroxy derivative of M-1916 that proved to be identical with one of the two isolated products of metabolism. γ-4-Hydroxycyclohexylbutyric acid (Paper VII) was acetylated (low yield) and the acetate X converted successfully through the acid chloride to the peroxide, which entered into the alkylation reaction in the

(1) Compare Fieser and Turner, THIS JOURNAL, **69**, 2338 (1947).

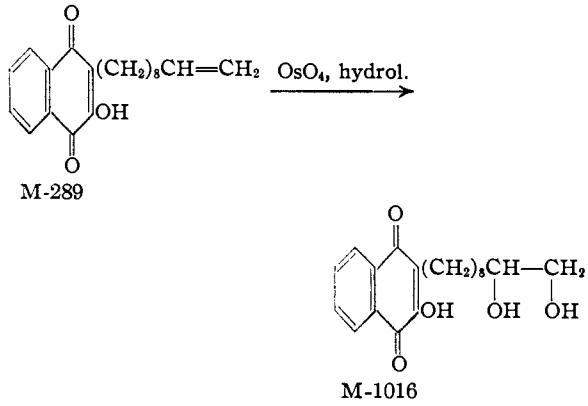
(2) Hooker, *J. Chem. Soc.*, **61**, 611 (1892).



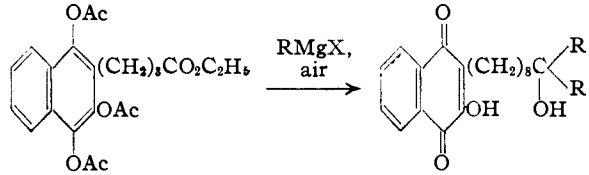
normal manner and gave the acetoxyquinone XI; from this the hydroxylated compound XII was easily obtained.



The next compound listed, M-1016, was prepared by hydroxylation of the decenyl derivative M-289 with osmium tetroxide; the yield was only 16% and was not improved by employing the acetate, although a corresponding hydroxylation of lapachol was successful only when the acetate was used.



Four of the remaining alcoholic derivatives were prepared by a Grignard synthesis from M-1917 hydroquinone triacetate. This ester triacetate on treatment with excess Grignard reagent was converted to the carbinol and deacetylated, and the resulting hydroquinone underwent ready air oxidation to the quinone. The dimethyl carbinol is a



crystalline solid; the three higher alcoholic quinones, as well as the homolog M-2376 prepared by Hooker oxidation, are oils at room temperature but could be obtained in analytically pure form by extraction from benzene with 65% methanol containing sodium carbonate.

Other Quinones.—Some of the remaining miscellaneous compounds were prepared from the products of peroxide alkylation with ω-bromo- and ω-cyanoundecylic acid; the bromo derivative condensed with diethylaniline to give M-379, and the nitrile was hydrogenated to the primary amine M-341. The methods used for obtaining the other compounds are indicated in the Table.

Experimental

Carboxyl Derivatives

M-1013 was prepared from **4-amino-2-carbethoxy-1,3-dihydroxynaphthalene**, made by coupling the carbethoxy-dihydroxy compound (9 g.) with diazotized sulfanilic acid, reducing the azo dye with sodium hydrosulfite, and crystallizing the amine hydrochloride from hydrochloric acid containing stannous chloride. The substance formed colorless or pinkish needles, dec. 190–210°; yield 7 g. (73%).

Anal. Calcd. for $C_{13}H_{14}O_4NCl$: N, 4.94. Found: N, 4.92.

Oxidation was carried out with dichromate in either aqueous or acetic acid solution and gave a yellow precipitate that on crystallization from benzene–ligroin afforded rosettes of light yellow needles. The needles on standing slowly turned to a red powder, m. p. 108–109°. The red form on recrystallization again gave yellow needles that sintered at 86–87° and melted at 108–109°. The yellow form was analyzed (Table XV).

TABLES XV–XVII

MISCELLANEOUS 2-HYDROXY-1,4-NAPHTHOQUINONES WITH SUBSTITUTED SIDE CHAINS

M-	Side chain	Formula	M. p., °C.	Prepd. by	Method	Yield, %	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
			XVa. CARBOXYL DERIVATIVES							
1013	$-CO_2C_2H_4$	$C_{14}H_{10}O_5$	108.8–109.4	E. B.	See text		63.41	63.25	4.09	4.10
1931	$-CH_2CH_2CO_2H$	$C_{11}H_{10}O_5$	195–196	C. H.	From ester	98	63.41	63.51	4.09	4.56
	Ethyl ester	$C_{15}H_{14}O_5$	135–136		From lactone	86	65.68	65.57	5.14	5.32
	Lactone	$C_{13}H_8O_4$	Dec. 280		PA, see text	45	68.40	68.73	3.53	3.64
1918	$-(CH_2)_4CO_2H$	$C_{14}H_{14}O_5$	160–161	C. H.	Ester + alc. KOH	85	65.66	65.82	5.14	5.44
	Ethyl ester	$C_{17}H_{18}O_5$	102–104		PA, see text		67.54	67.80	6.00	6.28
2232	Amide[a]	$C_{16}H_{15}O_4N$	178.5–179.5		$SOCl_2$; NH_4OH–acet.	50	65.92	65.91	5.53	5.15
1014	$-(CH_2)_3CH(CH_3)CO_2H$	$C_{16}H_{16}O_5$	183.5–185	W. R. V.	Hooker oxid.	90	66.65	66.83	5.60	5.82
	Methyl ester	$C_{17}H_{18}O_4$	76.5–78		MeOH–H_2SO_4		67.64	67.61	6.00	6.34
2233	$-(CH_2)_4CH(CH_3)CO_2H$	$C_{17}H_{18}O_5$	132–134	W. R. V.	PA, see text	44	67.64	67.63	6.00	6.23
	Metbyl ester	$C_{18}H_{20}O_5$	76.6–77.9		MeOH–H_2SO_4		68.34	68.61	6.37	6.60
2240	Amide[b]	$C_{17}H_{19}O_4N$	181–182		$SOCl_2$; NH_4OH–acet.	50	67.76	68.03	6.36	6.07
1015	$-(CH_2)_5CH(CH_3)CO_2H$	$C_{18}H_{20}O_5$	136.8–137.8	W. R. V.	PA, see text	48	67.76	68.36	6.36	6.57
	Methyl ester	$C_{19}H_{22}O_5$	80.8–83.6		MeOH–H_2SO_4		69.07	69.35	6.71	6.98
			XVb. ETHERS							
308	$-(CH_2)_4OC_4H_9$-*n*	$C_{18}H_{22}O_4$	77–78	M. B. M.	PA; from RCOCl	11	71.50	70.98	7.33	7.28
359	$-(CH_2)_{10}OCH_3$	$C_{21}H_{28}O_4$	82–84	K. E. H.	PA; from $(RCOO)_2$	48	73.23	73.57	8.19	8.21
			XVc. ALCOHOLIC DERIVATIVES							
100	$-CH_2C(OH)(CH_3)C_6H_{13}$-*n*	$C_{19}H_{24}O_4$	79.5–80.5	K. E. H.	See text		72.12	72.58	7.65	7.73
2336	$-(CH_2)_2$-4-Hydroxycyclohexyl	$C_{19}H_{22}O_4$	154.5–155.5	W. G. D.	See text		72.59	72.54	7.06	6.74
1016	$-(CH_2)_5CH(OH)CH_2OH$	$C_{20}H_{26}O_5$	124.5–125.5	M. F.	OsO_4		69.38	69.65	7.57	7.80
2231	$-(CH_2)_6C(OH)(CH_3)_2$	$C_{21}H_{28}O_4$	67.8–69.8	H. H.	Grig. syntb.	77.5	73.22	73.51	8.19	8.45
2343	$-(CH_2)_5C(OH)(C_4H_9$-*n*$)_2$	$C_{27}H_{40}O_4$	Oil	G. F.	Grig. synth.	83	75.65	75.41	9.53	9.34
	Hydroquinone tetraacetate	$C_{35}H_{48}O_8$	59–62		Red. acetylat.		70.20	70.56	8.42	8.78
2350	$-(CH_2)_5C(OH)(C_5H_{11}$-*n*$)_2$	$C_{29}H_{44}O_4$	Oil	G. F.	Grig. syntb.	76	76.28	75.96	9.71	9.72
2376	$-(CH_2)_6C(OH)(C_6H_{13}$-*n*$)_2$	$C_{29}H_{44}O_4$	Oil	G. F.	Two Hookers[c]	75	76.28	75.76	9.71	10.17
2367	$-(CH_2)_2C(OH)(C_6H_{13}$-*n*$)_2$	$C_{31}H_{48}O_4$	Oil	G. F.	Grig. synth.	71	76.81	77.37	9.98	10.07
			XVI. HALOGENATED SIDE CHAINS							
2247	$-(CH_2)_4Br$	$C_{14}H_{13}O_3Br$	103–104	M. W.	PA		54.39	54.71	4.24	4.47
2365	$-(CH_2)_2$-3-(CF_3)-cyclohexyl	$C_{19}H_{19}O_3F_3$	108.5–110	D. Y. C.[d]	PA; perox. 88%	59	64.77[e]	64.48	5.44	5.54
340	$-(CH_2)_{10}Br$	$C_{20}H_{25}O_3Br$	84–85	K. E. H.	PA; perox. 88%	49	61.07	61.09	6.41	6.39
			XVII. NITROGEN CONTAINING SIDE CHAINS							
2332	$-(CH_2)_4CONH_2$—See XVa									
2240	$-(CH_2)_4CH(CH_3)CONH_2$—see XVa									
	$-(CH_2)_{11}NH_2$	$C_{21}H_{29}O_2N$	dec. 270–300	K. E. H.	From hydrochloride		N, 4.08	N, 3.95		
341	Hydrochloride	$C_{21}H_{30}O_2NCl$	155–156		Hydrog. of M-335	72	N, 3.69	N, 3.47		
335	$-(CH_2)_{10}CN$	$C_{21}H_{25}O_2N$	96.5–97.5	K. E. H.	PA; perox. solid	59	N, 4.13	N, 4.27		
379	$-(CH_2)_{10}N(C_2H_5)_2$	$C_{24}H_{35}O_2N$	125–126	K. E. H.	M-340 + $(C_2H_5)_2NH$	100	N, 3.63	N, 3.58		
1943	$-CH[C_6H_4N(CH_3)_2$-*p*$]_2$	$C_{27}H_{36}O_2N$	174–175	E. B.	Michler's hydrol.	53	76.03	75.61	6.14	6.24

[a] Calcd.: N, 5.13; found: N, 4.99. [b] Calcd.: N, 4.65; found: N, 4.64. [c] By the procedure of Paper XII. [d] David Y. Curtin, Harvard University. [e] Calcd.: F, 16.18. Found (Tiedcke): F, 15.35, 15.69.

M-1931.—The half-peroxide of succinic acid was prepared[3] by shaking 15 g. of succinic anhydride with 37 cc. of 7.5% hydrogen peroxide for thirty-five minutes at a temperature below 30°. The yield of crystalline peroxide, m. p. 133° dec., was 13.0 g. (90%). A solution of 5 g. of the peroxide and 3.5 g. hydroxynaphthoquinone in 50 cc. of acetic acid gave off no gas when warmed on the steam-bath and hence 1 cc. of methanol was added and the solution refluxed for two hours. The yellow crystallizate that separated on cooling proved to be the lactone. Material that had been recrystallized from acetic acid (11.9 g.) was refluxed in 100 cc. of absolute ethanol with 10 cc. of 96% sulfuric acid for three hours and the mixture was diluted with water and the product taken into ether and extracted with bicarbonate. Acidification of the red extract gave 9 g. of yellow ester, m. p. 116–118°. The purified ester (4 g.) was refluxed for two hours with dilute potassium hydroxide, and when the solution was acidified and allowed to cool 3.5 g. of the acid separated as yellow crystals. An attempted alkylation in xylene was unsuccessful.

M-1918.—Alkylation in the usual way with the peroxide prepared in 60% yield by the sodium peroxide method from ethyl adipyl chloride gave a reddish oil from which yellow crystals of M-1918 ester separated; further processing of the residual oil afforded some of the free acid, identical with material obtained by saponification of the ester. The amide was obtained by refluxing the acid with thionyl chloride, removing the excess reagent *in vacuo*, and pouring an acetone solution of the residual oil into aqueous ammonia. The dark product that precipitated on dilution and acidification was taken up in methanol (20 cc.)–ether (50 cc.) and the solution clarified with charcoal and extracted with alkali; the crude amide that separated on acidification was crystallized from methanol.

M-2233.—The half-ester of α-methylpimelic acid[4] was prepared as follows. One mole of 2-carbethoxycyclohexanone was added to a solution prepared from 39.1 g. of potassium and 1 l. of absolute alcohol; 213 g. of methyl iodide was added and the mixture was stirred and warmed under reflux for one hour. About 600 cc. of distillate was then removed and the cooled mixture poured into water and extracted with ether. The solution was washed with bisulfite, dried, and the product distilled; the keto ester I was collected at 106.5–107.5° (10 mm.); yield 134 g. (74%); $n^{25}D$ 1.4530; ferric chloride test negative.

For cleavage to the diester II, 115 g. of I was refluxed for one and one-half hours with a solution prepared from

(3) Clover and Houghton, *Am. Chem. J.*, **32**, 65 (1904).

(4) von Auwers, Bahr and Frese, *Ann.*, **441**, 54 (1925).

2 g. of sodium and 125 cc. of ethanol. The recovered product boiled at 136.5–137.5° (10 mm.); yield 122.5 g. (85%). Partial saponification to III was accomplished by mixing a solution of 115 g. of diester in 515 cc. of alcohol with a solution of 28 g. of potassium hydroxide in 320 cc. of alcohol and adding a few drops of phenolphthalein solution. The color changed from red to pale orange after six hours at room temperature, and the solution was then concentrated to about 200 cc., diluted with water, and extracted thoroughly with ether to remove a little diester (15.5 g.). The aqueous layer was acidified and the half ester extracted with ether and distilled; b. p. 134.5–137° (1 mm.); yield 59.5 g. (59%). Treatment with thionyl chloride gave the acid chloride, b. p. 96–98° (1 mm.), and this with sodium peroxide gave the peroxide in 80–85% yield. Alkylation in the usual way afforded the crude quinone ester as an oil that was saponified by the procedure of Fieser and Turner[1] to M-2233. The product was crystallized from ligroin or more satisfactorily from methanol–water.

M-1015.—A solution of 32.9 g. of the half ester acid chloride of α-methylpimelic acid in 150 cc. of dry ether was added dropwise during three hours to an ice-cold solution of the diazomethane from 50 g. of N-nitrosomethylurea. The flask was removed from the ice-bath and the mixture allowed to stand overnight at room temperature and then filtered and evaporated at a temperature not over 30°. The residual yellow diazoketone (33.4 g.) was dissolved in 400 cc. of dioxane and added dropwise at 55° to a mixture of 400 cc. water, 4 g. freshly precipitated silver oxide, 10 g. sodium carbonate, 6 g. sodium thiosulfate and 1 g. of powdered glass. After one hour each at 55° and at 100° the product was recovered as a yellow oil (28 g.). It was esterified with ethanol–sulfuric acid (refluxed five hours) and the alkali-washed diester distilled (b. p. 129.5–133.5° (1 mm.), 177 g.) and partially saponified as in the preparation of the lower homolog III. The resulting half ethyl ester of α-methylsuberic acid was obtained as an almost colorless oil, b. p. 143–146° (1 mm.), yield 8.6 g. (25% over-all); neutralization equiv. 216.2 (calcd. 216.3). The acid chloride, b. p. 107–111° (1 mm.), afforded the peroxide in only 26% yield; the alkylation was conducted as described for M-2233. Hooker oxidation of M-1015 gave a product identical with M-2233 (anal. and mixed m. p.).

M-308.—The required **δ-*n*-butoxyvaleric acid** was prepared according to a general method of Hubacher.[5] A solution of 31 g. of δ-bromovaleric acid in 60 cc. of *n*-butanol was added slowly with stirring to a cooled solution prepared from 9.2 g. of sodium and 200 cc. of anhydrous *n*-butanol. The resulting thick mush was stirred continuously and the temperature was gradually raised to 80° and held there for one and one-half hours. The excess butanol was then removed by steam distillation and the residue acidified. An oily layer separated and failed to solidify and hence the product was collected in ether and distilled; b. p. 156–159° (17 mm.), $n^{23}D$ 1.4390; yield 6 g. (20%).

Anal. Calcd. for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 61.65; H, 10.26.

The acid chloride was prepared from 5.5 g. of acid, added at 0° to 10 cc. of purified thionyl chloride containing two drops of pyridine. The mixture was allowed to stand overnight, the excess reagent removed in vacuum (warm-water-bath) and the crude chloride converted directly to the peroxide.

M-359.—The intermediate ω-methoxyundecylic acid, b. p. 145° (0.5 mm.), m. p. 28–30°, was prepared by a known method.[6]

Alcoholic Derivatives. 1. Lapachone Synthesis: M-100

Ethyl β-Hydroxy-β-methylnonanoate (V).—A solution of 128 g. of freshly distilled commercial methyl hexyl ketone (b. p. 171–172° (742 mm.), $n^{24}D$ 1.4140) and 150 g. of pure ethyl bromoacetate in 200 cc. of dry benzene was added dropwise with stirring to 75 g. of activated granulated zinc. Refluxing began spontaneously and, after the addition was complete, was continued for one and one-half hours by heating on the steam-bath. The cooled mixture was treated with 400 cc. of 20% sulfuric acid, the layers were separated and the aqueous layer extracted once with benzene. The total benzene solution was washed with 5% sulfuric acid and with 10% sodium carbonate, dried, and the solvent removed. The hydroxy ester V distilled at 128–130° (12 mm.); $n^{22}D$ 1.4359; yield 151 g. (78%). The redistilled material boiled at 100–101° (1 mm.), $n^{23}D$ 1.4352.

Anal. Calcd. for $C_{12}H_{24}O_3$: C, 66.63; H, 11.18. Found: C, 66.64; H, 11.38.

β-Hydroxy-β-methylnonanoic acid (VI) was obtained by refluxing 40 g. of the ester for three hours with 330 cc. of 10% potassium hydroxide in absolute alcohol. The alcohol was removed in vacuum and a solution of the residue in 200 cc. of water was washed with ether, acidified, and the product recovered by ether extraction and distilled (slight decomposition); b. p. 142–144° (1 mm.), $n^{22}D$ 1.4514, yield 30 g. (89%).

Anal. Calcd. for $C_{10}H_{20}O_3$: C, 63.79; H, 10.71. Found: C, 63.60; H, 10.83.

3-Methyl-2-nonenoic Acid.—The hydroxy acid VI (29 g.) was refluxed for three hours with acetic anhydride (42 g.) and the product was collected by ether extraction and distilled: 16 g. (63%) of acid b. p. 120–121° (1 mm.), $n^{25}D$ 1.4636.

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.55; H, 10.65. Found: C, 70.56; H, 10.70.

This material did not decolorize bromine in carbon tetrachloride.

A solution of 40 g. of the hydroxy ester V in 150 cc. of benzene was refluxed with 36 g. of phosphorus pentoxide for three hours and the recovered unsaturated ester distilled; b. p. 83–88° (0.5 mm.), $n^{23}D$ 1.4420, yield 31 g. (85%). Hydrolysis, conducted as described above, gave 25 g. (95%) of unsaturated acid that did not decolorize bromine in carbon tetrachloride: b. p. 128–130° (4 mm.), $n^{24}D$ 1.4546.

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.55; H, 10.65. Found: C, 70.50; H, 10.61.

3-Methyl-3-nonenoic Acid VII.—Forty-eight grams of the hydroxy acid VI was treated with one drop of 36% hydrochloric acid and slowly distilled, with removal of the water formed. The product distilled at 120–130° (3 mm.); the redistilled acid boiled at 103–104° (0.3 mm.); $n^{25}D$ 1.4512; yield 38.5 g. (90%). The acid rapidly decolorizes bromine in carbon tetrachloride.

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.55; H, 10.65. Found: C, 70.65; H, 10.73.

2-Hydroxy-3-(β-methyl-β-octenyl)-1,4-naphthoquinone (VIII).—The acid chloride of VII (18.9 g.), b. p. 94–97° (9 mm.), on treatment with hydrogen peroxide and sodium hydroxide yielded only 4.6 g. of peroxide (titration). Alkylation of 2.4 g. of hydroxynaphthoquinone was conducted in the usual manner and the semisolid material precipitated by water was washed in ether with bicarbonate solution and the residue crystallized from Skelly-solve B. The yield of product m. p. 79–81° was 0.22 g., and the recrystallized quinone melted at 81°.

Anal. Calcd. for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.55; H, 7.40.

2-Hydroxy-3-(β-hydroxy-β-methyloctyl)-1,4-naphthoquinone (VIII, M-100).—A solution of 0.20 g. of VIII in 1 cc. of cold 96% sulfuric acid was allowed to stand for a few minutes and then diluted with 25 cc. of water and the product extracted with ether. Evaporation of the washed and dried solution left an orange-red oily residue that was refluxed for twenty-four hours with 10% alcoholic potassium hydroxide. The solvent was removed in vacuum and the residue treated with 100 cc. of 10% acetic acid; the oily product that separated was collected by ether extraction and obtained as a solid by trituration with pen-

(5) Hubacher, U. S. Patent 2,010,154, 1935.

(6) Hunsdiecker, *Ber.*, **75**, 1197 (1942).

tane. One crystallization from pentane gave 75 mg. of yellow solid and two further crystallizations gave material of satisfactory analysis (see Table). The substance depresses the m. p. of the unsaturated precursor VIII.

2. Alkylation with an Acetoxy Acid: M-2336[7]

γ-4-Acetoxycyclohexylbutyric Acid (X).—To a suspension of 25 g. of γ-4-hydroxycyclohexylbutyric acid in 25 cc. of dry pyridine 15 cc. of acetyl chloride was added in one portion. A vigorous exothermic reaction ensued and a white precipitate separated. The mixture was allowed to stand overnight and then treated with water and hydrochloric acid and the product was extracted with ether and distilled. A portion of the material distilled as a colorless liquid that promptly solidified; b. p. 149–151° (0.3 mm.); 12.2 g. Crystallization of the distillate from ligroin afforded 9.0 g. (29%) of white plates, m. p. 87–88°.

Anal. Calcd. for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 63.47; H, 9.17.

The distillation residue was insoluble in aqueous alkali but on saponification yielded some of the original hydroxy acid. Acetylation with acetic anhydride–sulfuric acid gave slightly higher yields in some experiment, but the results were erratic.

2-Hydroxy-3-(4-acetoxycyclohexyl)-propyl-1,4-naphthoquinone (XI).—The acid X (8.1 g.) was treated with oxalyl chloride (13.6 g.) and after the initial reaction had subsided the mixture was warmed on the steam-bath for four hours. The excess reagent was removed *in vacuo* and the acid chloride distilled, b. p. 133–134° (0.8 mm.); yield 5.8 g. (70%). The peroxide was obtained by the sodium peroxide method in almost quantitative yield, and alkylation of 2 g. of hydroxynaphthoquinone proceeded well; material recovered by evaporation, extraction from ether with bicarbonate to remove starting quinone and then colorless acid, and one crystallization from methanol amounted to 2.5 g. (63%), m. p. 109–111°. Concentration of the mother liquor and crystallization of the product from ligroin gave 1.1 g. of starting acid, m. p. 87–88°. The reaction product was submitted to extensive fractional crystallization, but only one isomer could be isolated and that in good yield. Material repeatedly crystallized from aqueous methanol and from ligroin (1.6 g., 37%) was obtained in dimorphic forms melting at 122–123° and 128–128.5°. When the low-melting form was immersed in a bath at 124.5° it melted immediately and then solidified at 125° and remelted at 128.2–128.5°. A mixture of the two forms behaved similarly.

Anal. Calcd. for $C_{21}H_{24}O_5$: C, 70.77; H, 6.79. Found: C, 70.79, 70.91; H, 6.86, 6.63.

2-Hydroxy-3-(4′-hydroxycyclohexyl)-propyl-1,4-naphthoquinone (M-2336).—A solution of 1 g. of the acetate and 0.1 g. of sodium methoxide in 25 cc. of methanol was allowed to stand at room temperature for eight hours; the red solution was acidified with 10 cc. of acetic acid and 0.25 cc. of 36% hydrochloric acid and warmed on the steam-bath to remove methanol. The washed and dried yellow precipitate sintered at 152.5° and melted at 154.5–155.5°, and when recrystallized from aqueous methanol it formed yellow needles of the same melting point without sintering; yield 0.83 g. (94%). An attempted inversion of the alcoholic derivative through the tosylate and acetate and hydrolysis (C. H.) gave largely unchanged starting material and a small amount of product identified by mixed melting point determination as Δ^2-unsaturated M-1916 (M-2333).

3. Hydroxylation[8]

M-1016.—A solution of 200 mg. of 2-hydroxy-3-*n*-decenyl-1,4-naphthoquinone (M-289) in 500 cc. of dry ether was treated with 170 mg. of osmium tetroxide and 1 cc. of pyridine in 20 cc. of ether. After the mixture had stood overnight the black precipitate of osmic ester that had separated was collected and refluxed with a suspension of 3 g. of sodium sulfite in 70 cc. of alcohol and 30 cc. of water. The red solution was filtered, acidified, and the product collected by ether extraction and crystallized from aqueous methanol; yield of product 36 mg. (16%), m. p. 124.5–125.5°.

By the same procedure lapachol acetate was converted into the known dihydroxyhydrolapachol (mixed m. p.) in low yield; lapachol itself could not be hydroxylated. A trial was made to see if the reaction could be used as the basis for the analysis of a mixture of saturated and unsaturated quinones by treating a known mixture of the acetates of lapachol and hydrolapachol with osmium tetroxide, hydrolyzing separately the precipitated material and that in the filtrate, and determining the hydroxylated and unhydroxylated quinones colorimetrically. The recovery of hydrolapachol was 83.5%, but the yield of diol was only 50%.

4. Grignard Synthesis

3-(8′-Carbethoxyoctyl)-1,2,4-triacetoxynaphthalene (M-1917 Hydroquinone Triacetate).—In the course of the preparation of repeated batches of M-1917,[1] it was found (G. F.) that the process can be greatly simplified and the yield improved by employing crude ethyl sebacyl chloride rather than distilled material. A solution of 40 g. of ethyl hydrogen sebacate, 40 g. of purified thionyl chloride and a few drops of pyridine in 100 cc. of anhydrous ether was refluxed for three hours with exclusion of moisture and the solution let stand overnight. The solution was evaporated at reduced pressure at a temperature not over 50°, a fresh 100-cc. portion of dry ether was added and the solvent evaporated again, and the residue was taken up in 250 cc. of ether and the solution filtered from pyridine hydrochloride and treated at −10° with 11.8 cc. of 34% hydrogen peroxide and then with a solution of 11.1 g. of sodium hydroxide in 40 cc. of water at a temperature of 5–10° (thirty minutes). At the end of the addition the aqueous layer was immediately tested for alkalinity and if not just weakly alkaline to litmus it was adjusted to this condition by the addition of acid or base (excess alkali causes troublesome emulsification and reduction in yield). After one-half hour of stirring at 0° and separation of the layers, the ethereal solution was washed with ice-cold water, dried and titrated; yield 0.0805 mole (92% from the half ester). When Eastman Kodak Co. thionyl chloride was used without purification the yield of peroxide was 15–20% less. Alkylation of 15 g. of hydroxynaphthoquinone in 180 cc. of acetic acid was conducted as usual at 90–95° (addition in forty minutes; at 95° for thirty minutes longer) and the product washed free from hydroxynaphthoquinone with sodium bicarbonate solution in ether and the recovered oil dissolved in 200 cc. of 70–90° ligroin; on stirring in a salt–ice-bath the product (M-1917) separated as a bright yellow powder, m. p. 67–70°, in a condition satisfactory for the next step; yield 16–18 g. (53–60%).

Reductive acetylation of 12.7 g. of M-1917 (with 12.7 g. of zinc dust, 85 cc. of acetic anhydride, 1.7 cc. of triethylamine) gave 11.15 g. (85.5%) of satisfactory hydroquinone triacetate as colorless prisms from 70–90° ligroin, m. p. 58–63° (all the compounds in this series melt over a range, probably owing to polymorphism). A sample recrystallized from 70–90° ligroin formed colorless prisms, m. p. 64–66°.

Anal. Calcd. for $C_{27}H_{34}O_8$: C, 66.65; H, 7.04. Found: C, 66.87; H, 7.20.

M-2231.—An ethereal solution of 18 g. of the triacetate was added to the methylmagnesium bromide solution from 14.2 g. (16 equiv.) of magnesium and the mixture was allowed to stand for three hours and decomposed with acid and water. The organic layer was dried and evaporated and the residue was dissolved in alcohol and the solution made alkaline and a stream of air bubbled through it for ten minutes. On acidification and dilution with water an oil separated and gradually solidified to give 9.85 g. (77.5%) of crude quinone, m. p. 54.64°. This material was extracted with hot ligroin and the solution decanted from some dark residual resin and allowed to stand for

(7) Work done at the University of California at Berkeley.

(8) Procedure of Criegee, Marchand and Wannowius, *Ann.*, **550**, 99 (1942).

several days in the cold room. The quinone tends to separate as an oil that very slowly crystallizes. Seven crystallizations gave 6.25 g. of light yellow crystalline solid, m. p. 56–63°. An analytical sample was further distilled at 100° (0.01 mm.) and crystallized again from ligroin, m. p. 56–63°.

M-2343.—A similar reaction was conducted with 18 g. (0.037 mole) of M-1917 hydroquinone triacetate and the reagent from 71 g. of *n*-butyl bromide and 12.5 g. (0.52 mole) of magnesium (refluxed six hours). The dark reddish ethereal extract of the reaction mixture turned yellow when merely shaken with air in a separatory funnel and the oil recovered from the ether was processed as follows: A solution of the material in 200 cc. of benzene was extracted repeatedly with an 0.8% solution of sodium carbonate in 65% methanol (about 1 l.) and the combined extract was washed with a total of 800 cc. of benzene in four portions. The aqueous methanolic solution was then diluted with an equal volume of brine and the sodium salt that separated as a red oil on the walls of the vessel was extracted with several portions of ether. The combined extract (800 cc.) was acidified with acetic or sulfuric acid (very dilute) and shaken until the color was canary yellow. The solution was then washed neutral to litmus, dried and evaporated. The residual yellow oil was dried in a desiccator over paraffin to remove a trace of benzene and was then in a satisfactory condition of purity; yield 13.5 g. (83%). Molecular distillation did not improve the material or give crystalline product. The sample for analysis was dried in a thin layer over paraffin in vacuum at 50°.

The di-*n*-amyl and di-*n*-hexyl carbinols M-2350 and M-2367 were prepared in exactly the same way and were also obtained pure without distillation.

M-2376 was prepared from M-2367 by two successive Hooker oxidations conducted by the first procedure given in Paper V (each copper sulfate oxidation was conducted at 25° for three hours). The reaction product was purified by extraction from benzene with 0.8% carbonate in 65% methanol as described above.

Halogenated Side Chains

The intermediates for M-2247 and M-340 were prepared by known methods: δ-bromovaleric acid,[9] acid chloride b. p. 116–118° (33–34 mm.); ω-bromoundecylic acid,[10] b. p. 170–175° (3 mm.), m. p. 46–48°, yield 58%.

γ-3-Trifluoromethylcyclohexylpropionic Acid was prepared by hydrogenation of the aromatic acid (paper VIII) in acetic acid in the presence of Adams catalyst; the yield of product, b. p. 108–109° (0.4 mm.), $n^{20}D$ 1.4295, was 91%. An analytical sample boiled at 110° (0.4 mm.), $n^{20}D$ 1.4298.

Anal. Calcd. for $C_{10}H_{15}O_2F_3$: C, 53.57; H, 6.74. Found: C, 53.41; H, 6.85.

The acid chloride boiled at 122–125° (16 mm.).

Nitrogen-Containing Side Chains

The side chain $—(CH_2)_{10}CN$ of **M-335** was introduced without difficulty with the peroxide from ω-cyanoundecylic acid[11] (m. p. 56–57°, yield 60%). Hydrogenation to the amine hydrochloride **M-341** was accomplished with a solution of 7.5 g. of 2-hydroxy-3-ω-cyanodecyl-1,4-naphthoquinone in 200 cc. of ethanol and 10 cc. of 36% hydrochloric acid in the presence initially of 2 g. of a 20% palladium–charcoal catalyst. Only one equivalent of hydrogen was absorbed in twelve hours at 2–3 atmospheres pressure, but after 0.1 g. of Adams catalyst had been added the hydrogenation went slowly to completion. The solution was filtered and evaporated in vacuum and water was added, whereupon a pale yellow precipitate separated. The salt was recrystallized from dilute acid. The free base was obtained by careful neutralization.

2-Hydroxy-3-ω-diethylaminodecyl-1,4-naphthoquinone (M-379) was prepared by refluxing a mixture of 2 g. of the bromide (M-340), 16 cc. of diethylamine and a trace of potassium iodide for fifteen hours. The supernatant liquid was decanted from the cooled mixture and the crystalline residue of salts washed with ether. The liquid and washings were evaporated on the steam-bath overnight and the dark red residue dissolved in 250 cc. of water and the *p*H adjusted to 6.5. The product separated as a dark red oil that slowly crystallized, and it was recrystallized from ethanol–water; yield 2 g.

2-Hydroxy-3-(N,N′-tetramethyl-*p*,*p*′-diaminodiphenyl)-1,4-naphthoquinone (M-1943).—The best variation of the general procedure[12] found in several trials was as follows: A solution of 4 g. of hydroxynaphthoquinone and 7 g. of Michler hydrol in 150 cc. of alcohol was refluxed for three hours and allowed to cool, when 6.6 g. of crystalline product separated. A further crop of 1.5 g. was obtained after concentration of the mother liquor; total yield of material, m. p. 172–175°, 82%. The best method found for purification was to dissolve the quinone in the minimum quantity of benzene, filter, add about two volumes of absolute alcohol, and boil the solution until a large crop of crystals had separated. The product collected after cooling amounted to a recovery of 60–70%. The quinone forms dark blue crystals and is soluble in both acid and alkali. The melting point seems to be dependent upon the rate of heating; the analytical sample melted at 162–164°, but other samples melted as high as 174–175°.

Summary

Hydroxynaphthoquinones with substituent groups of the types $—(CH_2)_nCO_2H$ and $—(CH_2)_nCH(CH_3)CO_2H$ were prepared with use of the peroxides of the half esters of the dibasic acids. Three methods were developed for the synthesis of quinones having alcoholic hydroxyl groups in the side chain. One of these (M-2336) proved to be identical with a product of the metabolic oxidation of the parent compound; another (M-2350) offers promise as a degradation-resistant compound of high antimalarial potency.

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(9) Hunsdiecker and Hunsdiecker, *Ber.*, **75**, 291 (1942).

(10) Perkins and Cruz, THIS JOURNAL, **49**, 1072 (1927).

(11) Perkins and Cruz, *ibid.*, **49**, 1073 (1927).

(12) Möblau and Klopfer, *Ber.*, **32**, 2146 (1899).

Naphthoquinone Antimalarials. IV–XI. Synthesis. XI. Related Compounds

This paper reports the results of a number of small projects that are too little related to one another to call for a general description. The compounds prepared for assay are listed in Table

TABLE XVIII

RELATED COMPOUNDS AND INTERMEDIATES

M-	Ref. no.	Compound NQ = 1,4-naphthoquinone	Formula	Prepd. by	M. p. or B. p. °C.	Mm.	Notes	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1743	1	2-Isoamyl-1,4-naphthoquinone	$C_{15}H_{16}O_2$	F. C. C.	m 46–47.5		3 + CrO_3 50° (26%)	78.91	79.25	7.07	7.27
	2	β-Tetralyl isobutyl ketone	$C_{18}H_{20}O$	H. H.	b 135	0.4	Fried.-Crafts CS_2 (78%)	83.28	83.11	9.32	9.40
		2,4-Dinitrophenylhydrazone	$C_{21}H_{24}O_4N_4$		m 172–173.5		Hexag. red leaflets	63.62	63.90	6.10	6.06
	3	β-Isoamylnaphthalene (crude)		F. C. C.	b 114–124	0.5	2 + Pd-C 310°: 50% (+ 4)				
	4	β-Napbthyl isobutyl ketone		H. H.	b 144–145	0.8	Fried.-Crafts in $C_6H_5NO_2$				
					Oxime m 96–99		Tbrough picrate 38%				
1900	5	2-Isoamyl-1,4-naphthoquinone oxide	$C_{15}H_{16}O_3$	F. C. C.	Molec. distn.		1 + H_2O_2–Na_2CO_3	73.75	73.52	6.59	6.59
	6	β-1',3'-Dimethylbutyl-naphtbalene	$C_{16}H_{20}$	H. H.	b 119–121	0.7	4 + CH_3MgBr; I_2;	90.51	90.30	9.49	9.62
					$n^{24}D$ 1.5610		Ni-hydrog. (81% overall)				
	7	2-(1',3'-Dimethylbutyl)-NQ	$C_{16}H_{18}O_2$	H. H.	Molec. distn.		6 + CrO_3 90° (38%)	79.31	78.79	7.31	7.30
	8	Oxide	$C_{16}H_{18}O_3$		Molec. distn.		H_2O_2–Na_2CO_3 (58%)	74.39	74.20	7.02	7.05
				Peroxide Alkylations (PA)							
1732	9	2-Methyl-3-isoamyl-NQ	$C_{16}H_{18}O_7$	F. C. C.	m 44.5–45		PA; sublimed	79.31	79.13	7.49	7.49
	10	2-Acetylamino-3-metbyl-NQ	$C_{13}H_{11}O_3N$	A. G. W.	m 157–158		Pb(OAc)$_4$ (74% crude)	68.11	68.03	4.84	4.65
	11	Free amine (known)	$C_{11}H_9O_2N$		m 166–166.5		96% H_2SO_4 at 90° (76%)	70.57	69.48	4.84	4.99
	12	2-Acetylamino-3-isobutyl-NQ	$C_{16}H_{17}O_4N$	A. G. W.	m 171–171.8		PA (44%)	71.00[a]	70.91	6.32	6.16
	13	Free amine	$C_{14}H_{15}O_2N$		n 95–96		96% H_2SO_4 at 25° (80%)	73.42	73.52	6.59	6.27
	14	2-Acetylamino-3-isoamyl-NQ	$C_{17}H_{19}O_3N$	A. G. W.	m 168.8–169		PA (42%)	71.55	71.36	6.71	6.30
1949	15	Free amine	$C_{15}H_{17}O_2N$		m 54–56		As for 13 (73%)	74.04	74.45	7.05	6.89
2318	16	2-δ-Cyclohexylbutyl-NQ	$C_{20}H_{24}O_2$	C. H.	m 74–75		PA (10%)	80.77	80.68	8.13	7.76
	17	2-γ-Cyclohexylpropyl-NQ	$C_{19}H_{22}O_2$	F. C. C.	m 75.6–76.2		PA (16%)	80.81	81.04	7.85	8.02
	18	2-Chloro-3-γ-cyclohexyl-propyl-NQ	$C_{19}H_{21}O_2Cl$	F. C. C.	m 115.5–116.5		PA (49%)	72.03	72.49	6.68	6.94
	19	2-Chloro-3-γ-*cis*-β-decalyl-NQ	$C_{23}H_{27}O_2Cl$	F. C. C.	m 114–116		PA (62%), see text	74.47	74.63	7.34	7.45
	20	2-Chloro-3-isoamyl-NQ	$C_{15}H_{15}O_2Cl$	H. H.	m 93–93.5		PA (55%); from EtOH	68.57	69.04	5.75	5.85
				Thio Derivatives							
	21	2-Mercapto-3-γ-cyclohexyl-propyl-1,4-naphthohydro-quinone triacetate	$C_{28}H_{30}O_6S$	F. C. C.	m 125.5–127.5		See text	67.84	68.17	6.83	7.02
	22	2-Acetomercapto-3-isoamyl-NQ	$C_{17}H_{20}O_3S$	F. C. C.	m 224–226		See text	67.08	67.13	6.62	6.54
				Bz-Substituted Hydroxynapbthoquinones							
2226	23	2-OH-6-methyl-3-isoamyl-NQ	$C_{11}H_8O_2$	E. W.	m 129.4–130.2		PA known quinone (24%)	74.39	74.40	7.02	7.32
2229	24	2-OH-7-methyl-3-isoamyl-NQ	$C_{11}H_8O_2$	E. W.	m 118–119		PA of No. 26 (56%)	74.39	74.37	7.02	7.24
	25	2-Hydroxy-3,6-dimethyl-NQ	$C_{12}H_{10}O_2$	E. W.	m 171.2–171.8		Quinone tbrough oxide	71.28	71.36	4.98	5.29
	26	2-Hydroxy-7-methyl-NQ	$C_{11}H_8O_2$	E. W.	m 206, dec.		Hooker ox. of No. 25	70.26	70.18	4.28	4.47
	27	2-OH-3-isoamyl-6-isohexyl-NQ	$C_{21}H_{28}O$	E. W.	m 65.8–66.6		PA of No. 31 (43%)	76.79	77.09	8.59	8.87
	28	2-Methoxy-6-isocaproyl-napbthalene[b]	$C_{14}H_{20}O_2$	E. W.	m 77–79		F.-C. in $C_6H_5NO_2$ (40%)	79.65	79.72	7.85	8.01
	29	2-Methoxy-6-isobexyl-naphthalene	$C_{17}H_{20}O$	E. W.	m 59–60		Clemm. redn.	84.25	84.41	9.15	9.51
	30	6-Isohexyl-2-naphthol	$C_{16}H_{20}O$	E. W.	m 79–79.8		29 + HBr–HOAc (89%)	84.16	83.97	8.83	9.09
	31	2-Hydroxy-6-isohexyl-NQ	$C_{16}H_{18}O_3$	E. W.	m 97–97.6		From No. 30, see text	74.39	74.42	7.02	7.16
2207	32	2,6-$(OH)_2$-3-γ-cyclohexyl-propyl-NQ	$C_{19}H_{22}O_4$	E. B.	m 268–269		PA (13.5%); EtOH	72.82	72.89	6.76	6.90
1957	33	2-HO-3-(3',7'-dimetbyloctyl)-6-Br-NQ	$C_{20}H_{29}O_3Br$	W. G. D.	m 138.4–139.4		PA (33.5%); MeOH	61.07	61.07	6.40	6.49
				Quinones of Other Types							
2248	34	2-OH-3-γ-Cyclohexylpropyl-5,6,7,8-tetrahydro-NQ	$C_{19}H_{26}O_3$	C. H.	m 85.5–86		M-1916, Pt, H_2, HOAc (88%); purple in alk.	75.46	75.84	8.67	8.92
	35	Triacetoxytetrabydro-naphthalene	$C_{16}H_{18}O_6$	C. H.	m 141–142		Thiele react. (78%)	62.74	63.24	5.92	6.17
	36	2-Hydroxy-5,6,7,8-tetrahydro-NQ	$C_{10}H_{10}O_3$	C. H.	m 141–142		Alc. HCl (N_2), Ag_2O	67.40	67.02	5.66	5.59
	37	5-Hydroxy-6-γ-cyclohexyl-propyl-4,7-tbionaphtbo-quinoue	$C_{17}H_{20}O_3S$	M. G. E.	m 104–105		PA (24%); purple in alk.	67.08	67.51	6.62	6.94
	38	3-Hydroxy-2-γ-cyclobexyl-propyl-1,4-phenanthrene-quinone	$C_{23}H_{26}O_3$	J. A. G.[d]	m 158.4–160		PA (35%); from HOAc	79.28	79.40	6.94	7.20

TABLE XVIII (*Continued*)

M-	Ref. no.	Compound NQ = 1,4-naphthoquinone	Formula	Prepd. by	M. p. or B. p. °C. Mm.	Notes	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
					Di-(2-hydroxy-1,4-naphthoquinonyl-3)-methanes					
1724	39	Parent compound	$C_{21}H_{12}O_6$	L. F. F.	m 249–251, dec.	Hydroxy-NQ, CH_2O, BF_3	70.00	69.99	3.36	3.45
		Diacetate	$C_{25}H_{16}O_8$		m 132–133	Ac_2O–H_2SO_4	67.45	67.52	3.63	3.71
272	40	*o*-Chlorophenyl derivative	$C_{27}H_{15}O_6Cl$	M. T. L.	m 235, dec.	Hydroxy-NQ, ArCHO, 90°	68.92	68.95	3.19	3.18
276	41	*p*-Chlorophenyl derivative	$C_{27}H_{15}O_6Cl$	M. T. L.	m 172–173	Yel. platelets	68.92	69.02	3.19	3.18
2245	42	*p*-Dimethylaminophenyl derivative	$C_{29}H_{20}O_6N$	E. B.	m 157–159	Orange needles. C_6H_6	72.64	72.04	4.41	4.96
					Other Compounds					
1905	43	2-Hydroxy-3-*p*-chloroanilino-NQ	$C_{16}H_{10}O_3NCl$	C. H.	m 270.5–271	NQ oxide + $ArNH_2$	64.12	64.10	3.36	3.32
	44	2-β-Diethylaminoethylamino-NQ	$C_{16}H_{20}O_2N_2$	F. C. C.	m 85.5–86.5	Methoxy-NQ + RNH_2	70.56[a]	70.28	7.40	7.09
	45	2-N-Morpholino-1,4-naphthoquinone	$C_{14}H_{13}O_3N$	F. C. C.	m 164–165	See No. 44	69.12	69.40	5.38	5.49
	46	2-β-Hydroxyethylamino-NQ	$C_{12}H_{11}O_3N$	F. C. C.	m 159.5–160.2	See No. 44	66.35	66.75	5.10	5.08
	47	4-Cyanamino-1,2-naphthoquinone	$C_{11}H_6O_2N_2$	F. C. C.	m 231, dec.	NQ sulfonate + $CaCN_2$	66.66[b]	66.30	3.05	3.33
	48	4-Ureayl-1,2-naphthohydr. diacet.	$C_{15}H_{14}O_5N_2$	F. C. C.	m 208.5–209	From No. 47, see text	59.60[c]	59.43	4.67	4.44

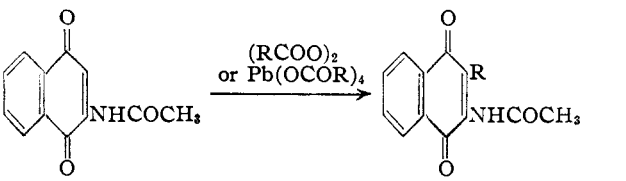
[a] Calcd.: N, 5.17. Found: N, 4.92. [b] Oxidation with alkaline ferricyanide gave an acid corresponding in analysis and m. p. (202–204°) to 2-methoxynaphthalene-6-carboxylic acid. [c] Calcd.: Br, 20.32. Found: Br, 20.31. [d] James A. Gibbs, Jr. [e] Calcd.: N, 10.29. Found: N, 10.02. [f] Calcd.: N, 14.14. Found: N, 13.98. [g] Calcd.: N, 9.27. Found: N, 9.48.

XVIII along with intermediates and related substances, and supplementary explanations and data are given in the Experimental Part. The compound numbers entered in the second column are used for cross reference.

Experimental

2-Isoamyl-1,4-naphthoquinone and Derivatives. Nos. 1–8.—The synthesis of desoxyhydrolapachol (No. 1) was accomplished through the intermediates 2 and 3. The ketone obtained in good yield by a Friedel–Crafts reaction of tetralin and isovaleryl chloride[1] was submitted to the dehydrogenation–disproportionation process of Newman and Zahm.[2] This proceeded poorly and gave a mixture of the desired aromatic hydrocarbon (No. 3) and the aromatic ketone (No. 4); the latter was obtained more satisfactorily by condensation of naphthalene with isovaleryl chloride in nitrobenzene.[3] Oxidation of the hydrocarbon 3 gave the quinone 1, and this was converted by the action of sulfuric acid on the oxide 5 into a product, m. p. 89–91°, that did not depress the m. p. of hydrolapachol. The quinone 7 and its oxide 8 were prepared in order to synthesize the α-methyl derivative of hydrolapachol, but no definite products could be isolated from attempts to hydrolyze this oxide with either acidic or basic agents; the behavior is like that of the similarly α-substituted 2-cyclohexyl-1,4-naphthoquinone oxide (Paper III). In the preparation of the dimethylbutylnaphthalene 6, various methods of dehydrating the carbinol were discarded in favor of brief heating (15 min.) with 0.5% iodine; the material was then washed successively in ethyl acetate with alkali, bisulfite, bicarbonate and water, dried and hydrogenated.

Peroxide Alkylations. Nos. 9–20.—Most of the quinones of this series were made by the reaction of a 1,4-naphthoquinone with an appropriate diacyl peroxide in the usual fashion. The compounds 10, 12 and 14 were obtained with the use of 2-acetylamino-1,4-naphthoquinone as the acceptor in alkylations with a peroxide or with lead tetraacetate (with malonic acid as promoter). The free amine cannot be used because it suffers oxidation, but the reaction proceeds well with the acetate and the course of the alkylation can be followed by the Craven test[4]; if a batch



of either 12 or 14 gives a positive test it can be purified by digestion with hot bisulfite solution, which dissolves the starting material but not the product. The methyl homolog 10 itself dissolved in bisulfite solution and was purified by several crystallizations from dilute methanol and from ligroin and by sublimation at 1×10^{-5} mm. The free 2-amino-3-methyl-1,4-naphthoquinone has a slightly higher m. p. than reported in the literature.[5]

The two peroxide alkylations of 1,4-naphthoquinone (16, 17) afforded the monoalkyl derivatives in only very low yield. A curious observation (M. F.) is that a suspension of 5 g. of potassium 1,4-naphthoquinone-2-sulfonate in 700 cc. of acetic acid reacted with 0.018 mole of di-(cyclohexylbutyryl) peroxide to give in 14% yield a product, m. p. 76–77°, identified by analysis and mixed m. p. as 2-γ-cyclohexylpropyl-1,4-naphthoquinone, No. 17. The three alkylations of 2-chloro-1,4-naphthoquinone (18, 19, 20) gave results so satisfactory as to suggest that this may be a better acceptor than the hydroxy compound. Hydrolysis of the chloro derivatives with boiling methanol and sodium hydroxide by the procedure given in Paper III gave in high yield products identical with M-1916, M-2279 (same melting range), and M-1523. The 2-chloro-3-alkyl derivatives are so much more resistant to alkali under mild conditions that a separation of alkylated from unalkylated material can be effected very simply. Thus in the preparation of No. 19 from 0.93 mole of peroxide and 18 g. of chloronaphthoquinone a first crop of 17.0 g. of crystalline product (m. p. 114–116°) separated from the reaction solution and the mother liquor material was taken into ether and the solution extracted repeatedly with 2 *N* sodium hydroxide until the initially red extracts became

(1) Procedure similar to those of Barbot, *Bull. soc. chim.*, [4] **47**, 1314 (1930), and Karrer and Epprecht, *Helv. Chim. Acta*, **23**, 272 (1940).

(2) Newman and Zahm, THIS JOURNAL, **65**, 1097 (1943).

(3) Rousset, *Bull. soc. chim.*, [3] **15**, 69 (1896); [3] **17**, 313 (1897), used carbon bisulfide.

(4) Craven, *J. Chem. Soc.*, 1605 (1931).

(5) Baker, Davies, McElroy and Carlson, THIS JOURNAL, **64**, 1099 (1942).

almost colorless. The material recovered from the ether layer on crystallization from petroleum ether afforded 3.5 g. of satisfactory product, m. p. 105–111°.

Thio Derivatives.—It has been observed that 2-halo-3-alkyl-1,4-naphthoquinones give an extremely sensitive color test with sodium sulfide. When a drop of a freshly prepared solution of crystalline sodium sulfide is added to a solution of a crystal or two of the quinone in alcohol or acetone an intense color develops immediately and persists for at least six hours. The solution in alcohol is purple, that in acetone is blue or purplish blue. The quinones 18, 19 and 20 all give the test, as do 2-chloro- and 2-bromo-3-cyclohexyl-1,4-naphthoquinone. Chloronaphthoquinone gives a transient color that changes to brown after a few minutes, and hence an alkylated and unalkylated product can be distinguished. 2,3-Dichloro-1,4-naphthoquinone gives a purple color changing to red in ten to fifteen minutes. From a rough comparison it appeared that this test is less sensitive than the plumbite test for the detection of sulfide ion.

Fries and Kerkow[6] found that 2-anilino-3-chloro-1,4-naphthoquinone reacts readily in alcoholic solution with aqueous sodium sulfide to give a deep blue solution containing the 2-anilino-3-mercapto derivative; this could not be isolated as such but underwent ready air oxidation to a pentacyclic quinone. That a similar replacement of chlorine by sulfhydryl occurs in the present instance was established by the isolation of the crystalline triacetyl derivative No. 21 as follows.

A warm, filtered solution of 7.5 g. of sodium sulfide crystals in 10 cc. of water was added to a solution of 3 g. of 2-chloro-3-cyclohexyl-1,4-naphthoquinone in 200 cc. of alcohol and after four minutes the deep violet solution was cooled and acidified with 3 *N* hydrochloric acid. A small amount of sulfur separated overnight and was removed by filtration; water saturated with hydrogen sulfide was added to prevent oxidation, and on cooling in ice a crop of slightly yellowish crystals of the sulfhydryl hydroquinone deposited and was collected by centrifugation in a Skau tube and dried in a vacuum desiccator (1.16 g., m. p. 152–155°). An additional crop of 0.82 g. of material was obtained from the mother liquor. The initially weakly colored material darkened rapidly on storage in a desiccator; a sample kept for a few months was deep orange but still crystalline, and it still gave a purple color with sodium hydroxide in alcohol. A freshly prepared sample submitted for assay in an oxygen-free vessel showed only slight antimalarial activity. The triacetate No. 21 was prepared by acetylation in the presence of zinc dust and triethylamine without application of heat. The resulting solid was deposited from alcohol in poorly-shaped, cream-colored crystals, but recrystallization from 30–60° petroleum ether gave rosettes of colorless needles.

Compound No. 22 was obtained from a solution of 1.5 g. of 2-isoamyl-1,4-naphthoquinone and 1.7 cc. of thioacetic acid in 10 cc. of alcohol; on standing overnight the solution lightened to a straw yellow and, after several days at 5°, large almost colorless crystals had separated. Recrystallization from methanol gave slightly yellowish crystals, m. p. 224–226°. The substance gives a typical purple color when treated with alcoholic alkali.

Bz-Substituted Hydroxynaphthoquinones.—The 6-methyl derivative of hydrolapachol, No. 23, was obtained by peroxide alkylation of 2-hydroxy-6-methyl-1,4-naphthoquinone, available from 2,6-dimethylnaphthalene by a process involving elimination of the quinonoid methyl group by Hooker oxidation.[7] The 7-methyl isomer, No. 26, was prepared similarly from 2,7-dimethylnaphthalene and alkylated to give No. 24. The synthesis of the 6-isohexyl derivative of hydrolapachol, No. 27, was accomplished through the intermediates 28–31. Of various processes tried for the conversion of the β-naphthol derivative 30 to the hydroxynaphthoquinone 31 the most satisfactory consisted in preparation of the β-naphthoquinone (yellow oil; by coupling, reduction to the amine and oxidation with ferric chloride), treatment of this with sodium bisulfite, and air oxidation of an alkaline solution of the resulting hydroquinone sulfonic acid.[8] The final product of the synthesis, No. 27, showed no antirespiratory activity against succinate oxidase.

No. 32, the 6-hydroxy derivative of M-1916, was obtained by peroxide alkylation of 2,6-dihydroxy-1,4-naphthoquinone.[9] Two attempts to alkylate the 2,7-isomer were unsuccessful.

Quinones of Other Types.—Compound No. 34, the tetrahydro derivative of M-1916, was obtained easily by the catalytic hydrogenation of M-1916; the substance forms orange crystals from petroleum ether. Attempts to alkylate No. 36, the tetrahydride of hydroxynaphthoquinone were unsuccessful.

Compound No. 37, the thiophene isolog of M-1916, was synthesized by peroxide alkylation of 5-hydroxy-4,7-thionaphthoquinone.[10] 4,7-Thionaphthoquinone was obtained from 4-(2-thienyl)-butyryl chloride by the prescribed procedure in 13% over-all yield. The Thiele reaction was conducted in lots of not more than 1 g. and the temperature was controlled to 58–60°; yield 60%. Conversion to the hydroxy quinone was best accomplished by refluxing the triacetate (2.25 g.) with alcohol (10 cc.) and 36% hydrochloric acid (2 cc.) under nitrogen and oxidizing the hydrolyzate in ether with silver oxide; yield 1.1 g. (84%).

The phenanthrene derivative No. 38 was prepared by alkylation of 3-hydroxy-1,4-phenanthrenequinone[11]; this intermediate when purified by sublimation melted at 202.8–205° (anal. correct).

Di-(2-hydroxy-1,4-naphthoquinonyl-3)-methane (No. 39) was prepared by adding 1 cc. of formalin and 1 cc. of boron fluoride etherate to a warm solution of 1.74 g. of pure hydroxynaphthoquinone in 25 cc. of acetic acid, filtering quickly, and heating the solution, from which golden plates soon began to separate, for one and one-half hours on the steam-bath. The material collected after cooling amounted to 1.15 g. and was satisfactory for analysis; when the mother liquor was heated further with 1 cc. more catalyst another crop of 0.30 g. separated; yield 81%. When 2 cc. of 36% hydrochloric acid was used as catalyst the yield was only 36%. The compound was very sparingly soluble in the usual solvents and forms golden plates from nitrobenzene.

The *o*-chlorophenyl derivative No. 40 was prepared, following the procedure of Hooker and Carnell,[12] by heating 10.44 g. of hydroxynaphthoquinone, 12 g. of *o*-chlorobenzaldehyde, and 40 cc. of alcohol in a pressure bottle on the steam-bath for forty-five minutes. The cooled mixture was diluted with 150 cc. of alcohol and the large yellow needles collected; yield in the first crop 4.8 g. The substance was recrystallized from absolute alcohol. No. 41 was prepared similarly from *p*-chlorobenzaldehyde (first crop 7.8 g.). No. 42 was obtained in the same way but without the use of a pressure bottle.

Other Compounds.—No. 43 was prepared by heating 0.5 g. of α-naphthoquinone oxide (Paper III) with 1.5 cc. of *p*-chloroaniline on the steam-bath; the mixture rapidly turned dark and after fifteen minutes was poured into 10 cc. of dilute hydrochloric acid. The bluish-grey precipitate on one crystallization from acetic acid gave 0.85 g. (98%) of purple needles, m. p. 269–270°. 2-Hydroxy-3-anilino-1,4-naphthoquinone[13] was obtained by the same procedure in 86% yield; purple needles, m. p. 210–210.5°.

2-β-Diethylaminoethylamino-1,4-naphthoquinone (No. 44).[14]—A suspension of 5 g. of 2-methoxy-1,4-naphtho-

(6) Fries and Kerkow, *Ann.*, **427**, 281 (1922).

(7) Fieser, Hartwell and Seligman, THIS JOURNAL, **58**, 1223 (1936).

(8) Friedländer, *Fortschr. Teerfarb. Fabr.*, **3**, 503 (1893).

(9) Dimroth and Kerkovius, *Ann.*, **399**, 36 (1913).

(10) Fieser and Kennelly, THIS JOURNAL, **57**, 1611 (1935).

(11) Fieser, *ibid.*, **51**, 940 (1929).

(12) Hooker and Carnell, *J. Chem. Soc.*, **65**, 76 (1894).

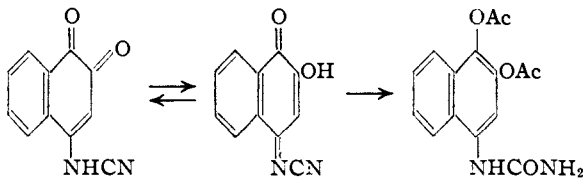
(13) Zincke and Wiegand, *Ann.*, **286**, 76 (1895).

(14) Based upon a procedure of Fieser and Fieser, THIS JOURNAL, **57**, 491 (1935).

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

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

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



No. 47 No. 48

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

Summary

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

CAMBRIDGE 38, MASS. RECEIVED MAY 13, 1947

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

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

BY LOUIS F. FIESER AND MARY FIESER

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

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

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

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

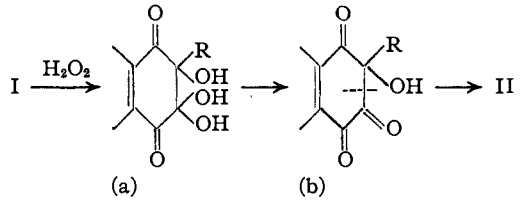
(2) Hooker, THIS JOURNAL, **58**, 1163, 1174, 1179 (1936).

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

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

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

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



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