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55. *Potential Anti-tumour Agents. Part II.*[1] *Polyporic Acid Series.*

By B. F. Cain.

A series of substituted quinones related to polyporic acid has been prepared for evaluation against rodent-tumour systems. Limited correlations between structure and activity are made.

As an extension to the work reported in Part I[1] a further series of quinones related to polyporic acid has been prepared. The materials described here have been prepared in order to investigate the effect of changing the electron density in the central quinone ring and varying the lipophilic properties.

Monosubstituted polyporic derivations have been prepared by arylation of 3,6-dichloro-2-phenyl-1,4-benzoquinone with aryl diazoacetates; the resultant 5-aryl dichloro-2-phenylquinones were readily hydrolysed by aqueous-methanolic potassium hydroxide to the dihydroxyquinones. Symmetrically disubstituted derivatives were made by similar arylation of 2,6-dichloro-1,4-benzoquinone.

The *p*-alkylanilines required for synthesis of some of these materials were conveniently prepared by rearrangement of the *N*-alkylanilines.[2] Difficulty was experienced with diazotization of some of the bases of higher molecular weight owing to insolubility of their salts and their derived diazonium salts; this was overcome by preparing the *N*-acetyl derivatives and from these the *N*-nitrosoacetamides which served directly as a source of diazoacetate and could be used without the necessity of buffering the solution with sodium acetate. This is the method of choice for preparing these compounds, if it is possible to obtain the *N*-nitrosoacetamide.

The compounds having n-alkyl and ω-phenylalkyl side chains in place of one phenyl ring of polyporic acid were prepared by adaptation of Fieser and Oxford's alkylation method.[3] In this method intermediates which were more easily manipulated were obtained by treating

[1] Part I, *J.*, 1961, 936.
[2] Hickinbottom, *J.*, 1937, 1120.
[3] Fieser and Oxford, *J. Amer. Chem. Soc.*, 1942, **64**, 2060.

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the acyl peroxide with the dichloroquinone rather than with the corresponding dihydroxyquinone. The ω-phenylalkanoic acids and the ω-phenylalkanoyl peroxides required were prepared by the procedures described by Fieser *et al.*[4]

By using the acute lymphocytic leukemia L1210 in mice, under standard conditions, as a test system it can be shown that, of the derivatives described here and in Part I,[1] those which have strong electron-donating or -attracting substituents are inactive. Those with less powerful substituents (halogen, alkoxyl, alkyl) retain anti-leukemic activity in some degree. One phenyl ring may be replaced by another hydrocarbon substituent (n-alkyl, ω-phenylalkyl) and activity still be retained. Progressive homologation of an alkyl side chain first increases and then decreases anti-leukemic effectiveness. The most active of the derivatives described so far, under the test conditions used, is 2-*p*-ethylphenyl-3,6-dihydroxy-5-phenyl-1,4-benzoquinone.

Experimental

3,6-*Dichloro*-2-p-*tolyl*-1,4-*benzoquinone*.—To a vigorously stirred solution of 2,5-dichloro-1,4-benzoquinone (35·4 g.) in ethanol (800 ml.) and ether (800 ml.) was added a solution of toluene-*p*-diazonium chloride (1·1 mol.), prepared in the minimum volume of water, together with sufficient aqueous sodium acetate to neutralize the excess of mineral acid present in the diazonium solution. After 2 hours' stirring, the solution was evaporated to 500 ml. and a crude product precipitated with water (1 l.). This solid was extracted with boiling 1 : 4 aqueous

2,5-Dichloro-1,4-benzoquinones.

				Found (%)				Required (%)		
3-Subst.	6-Subst.	Solvent*	M. p.	C	H	Cl ‡	Formula	C	H	Cl ‡
Ph	*o*-Tolyl	MeOH	143—144°	66·2	3·2	20·8	$C_{19}H_{12}Cl_2O_2$	66·5	3·5	20·7
,,	*m*-Tolyl	EtOH	180—181	66·1	3·2	20·7	$C_{19}H_{12}Cl_2O_2$	66·5	3·5	20·7
,,	*p*-Tolyl	HOAc	212—213	66·4	3·6	20·7	$C_{19}H_{12}Cl_2O_2$	66·5	3·5	20·7
o-Tolyl	*o*-Tolyl	EtOH	171—173	66·9	3·9	19·6	$C_{20}H_{14}Cl_2O_2$	67·2	3·9	19·8
m-Tolyl	*m*-Tolyl	EtOH	217—218	67·0	3·8	19·7	$C_{20}H_{14}Cl_2O_2$	67·2	3·9	19·8
p-Tolyl	*p*-Tolyl	HOAc	288—290	66·9	3·9	19·7	$C_{20}H_{14}Cl_2O_2$	67·2	3·9	19·8
o-C_6H_4Cl	Ph	EtOH	188—191	59·1	2·3	29·1	$C_{18}H_9Cl_3O_2$	59·4	2·5	29·3
m-C_6H_4Cl	,,	EtOH	188—189	59·5	2·6	29·2	$C_{18}H_9Cl_3O_2$	59·4	2·5	29·3
p-C_6H_4Cl	,,	Bu^nOH	234—235	59·6	2·6	29·3	$C_{18}H_9Cl_3O_2$	59·4	2·5	29·3
,,	*p*-Tolyl	A	235—236	60·8	2·9	27·9	$C_{19}H_{11}Cl_3O_2$	60·4	2·9	28·2
p-C_6H_4Br	,,	A	255—256	54·4	2·3	(35·3)	$C_{19}H_{11}BrCl_2O_2$	54·1	2·6	(35·7)
p-C_6H_4F	,,	EtOH	273—274	63·0	3·0	—	$C_{19}H_{11}Cl_2FO_2$	63·2	3·1	—
p-C_6H_4·OMe	,,	A	268—269	64·2	3·6	19·0	$C_{20}H_{14}Cl_2O_3$	64·4	3·8	19·0
p-C_6H_4·OAc	,,	A	240—242	62·7	3·6	17·5	$C_{21}H_{14}Cl_2O_4$	62·9	3·5	17·7
p-C_6H_4F	Ph	EtOH	280—281	62·2	2·7	—	$C_{18}H_9Cl_2FO_2$	62·3	2·6	—
p-C_6H_4I	,,	Bu^nOH	228—229	47·6	2·2	—	$C_{18}H_9Cl_2IO_2$	47·5	2·0	—
p-C_6H_4Cl	*p*-C_6H_4Cl	B	295—296	54·5	2·0	35·2	$C_{18}H_8Cl_4O_2$	54·3	2·0	35·6
p-C_6H_4Br	*p*-C_6H_4Br	A	303—304	44·3	1·8	(48·0)	$C_{18}H_8Br_2Cl_2O_2$	44·4	2·1	(47·4)
p-C_6H_4·OMe	*p*-C_6H_4·OMe	A	258—259†	61·7	3·5	18·4	$C_{20}H_{14}Cl_2O_4$	61·7	3·6	18·2
p-C_6H_4Et	Ph	C	205—206	67·0	3·7	19·6	$C_{20}H_{14}Cl_2O_2$	67·2	3·9	19·8
p-$C_6H_4Pr^n$	,,	Bu^nOH	149—150	67·6	4·4	19·1	$C_{21}H_{16}Cl_2O_2$	67·9	4·3	19·1
p-$C_6H_4Bu^n$	,,	Bu^nOH	156—157	68·6	4·6	18·3	$C_{22}H_{18}Cl_2O_2$	68·6	4·7	18·4
p-C_6H_4·C_5H_{11}	,,	EtOH	132—133	69·0	4·9	17·9	$C_{23}H_{20}Cl_2O_2$	69·2	5·1	17·8
p-C_6H_4·C_6H_{13}	,,	EtOH	137—138	69·6	5·5	17·1	$C_{24}H_{22}Cl_2O_2$	69·7	5·4	17·2
p-Tolyl	*p*-Tolyl	AcOH	288—289	67·0	3·7	19·7	$C_{20}H_{14}Cl_2O_2$	67·2	3·9	19·8
p-C_6H_4Et	,,	D	270—271	67·7	4·3	19·1	$C_{21}H_{16}Cl_2O_2$	67·9	4·3	19·1
p-$C_6H_4Pr^n$	,,	A	202—203	68·5	4·7	18·3	$C_{22}H_{18}Cl_2O_2$	68·6	4·7	18·4
p-$C_6H_4Bu^n$	,,	A	182—183	69·1	5·0	17·7	$C_{23}H_{20}Cl_2O_2$	69·2	5·1	17·8
p-C_6H_4·OMe	Ph	EtOH	184—186	63·4	3·1	19·6	$C_{19}H_{12}Cl_2O_3$	63·5	3·1	19·7
p-C_6H_4·OEt	,,	EtOH	159—160	64·1	3·7	19·1	$C_{20}H_{14}Cl_2O_3$	64·4	3·8	19·0
p-C_6H_4·OPr^n	,,	EtOH	159—160	65·0	4·3	18·4	$C_{21}H_{16}Cl_2O_3$	65·1	4·2	18·3
p-C_6H_4·OBu^n	,,	EtOH	157—158	65·6	4·4	17·6	$C_{22}H_{18}Cl_2O_3$	65·9	4·5	17·7
p-C_6H_4·OC_5H_{11}	,,	EtOH	158—159	66·1	4·7	17·3	$C_{23}H_{20}Cl_2O_3$	66·5	4·9	17·1
p-C_6H_4·OC_6H_{13}	,,	EtOH	154—156	67·0	5·0	16·7	$C_{24}H_{22}Cl_2O_3$	67·1	5·2	16·5

* A = Ethylene glycol monoethyl ether. B = Ethylene glycol diacetate. C = Diethylene glycol. D = Diethylene glycol monoethyl ether. † Derivative of atromentin; Akagi (*J. Pharm. Soc. Japan*, 1942, **62**, 191) gives m. p. **253—254°**. ‡ Figures in parentheses are for total halogen.

[4] Fieser *et al.*, *J. Amer. Chem. Soc.*, 1948, **70**, 3174.

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2,5-Dihydroxy-1,4-benzoquinones.

3-Subst.	6-Subst.	Solvent	M. p.	Found (%) C	Found (%) H	Formula	Reqd. (%) C	Reqd. (%) H
Ph	*o*-Tolyl	Pyridine	305—306	74·2	4·3	$C_{19}H_{14}O_4$	74·5	4·6
,,	*m*-Tolyl	Pyridine	246—247	74·3	4·4	$C_{19}H_{14}O_4$	74·5	4·6
,,	*p*-Tolyl	Pyridine	259—260	74·4	4·3	$C_{19}H_{14}O_4$	74·5	4·6
o-Tolyl	*o*-Tolyl	Pyridine	237—238	74·8	4·8	$C_{20}H_{16}O_4$	75·0	5·0
m-Tolyl	*m*-Tolyl	Pyridine	210—211	74·9	4·7	$C_{20}H_{16}O_4$	75·0	5·0
p-Tolyl	*p*-Tolyl	Pyridine	289—290	74·9	4·9	$C_{20}H_{16}O_4$	75·0	5·0
o-C_6H_4Cl	Ph	Toluene	307—308	66·1	3·2	$C_{18}H_{11}ClO_4$	66·2	3·4
m-C_6H_4Cl	,,	Toluene	245—247	66·1	3·3	$C_{18}H_{11}ClO_4$	66·2	3·4
p-C_6H_4Cl	,,	Toluene	289—291	66·0	3·4	$C_{18}H_{11}ClO_4$	66·2	3·4
,,	Tolyl	Pyridine	293—294	67·0	4·0	$C_{19}H_{13}ClO_4$ **	67·0	3·8
p-C_6H_4Br	,,	Pyridine	303—304	59·9	3·4	$C_{19}H_{13}BrO_4$ ††	59·3	3·4
p-C_6H_4F	,,	Pyridine	284—286	70·1	3·9	$C_{19}H_{13}FO_4$	70·4	4·0
p-C_6H_4·OMe	,,	Pyridine	265—266	71·2	4·6	$C_{20}H_{16}O_5$	71·4	4·8
p-C_6H_4·OH	,,	Pyridine	296—298	70·6	4·2	$C_{19}H_{14}O_5$	70·8	4·4
p-C_6H_4F	Ph	Dioxan	296—297	71·8	3·5	$C_{18}H_{11}FO_4$	72·0	3·7
p-C_6H_4I	,,	Toluene	272—273	51·6	2·7	$C_{18}H_{11}IO_4$	51·7	2·6
p-C_6H_4Cl	*p*-C_6H_4Cl	Pyridine *	305—306	60·2	2·9	$C_{18}H_{10}Cl_2O_4$ ‡‡	60·0	2·8
p-C_6H_4Br	*p*-C_6H_4Br	Pyridine *	311 †	55·3	3·1	$C_{18}H_{10}BrO_4$ §, ‖	55·3	3·3
p-C_6H_4·OMe	*p*-C_6H_4·OMe	Pyridine	295—297 ‡	68·1	4·4	$C_{20}H_{16}O_6$	68·2	4·6
p-C_6H_4Et	Ph	Pyridine	243—245	74·7	4·9	$C_{20}H_{16}O_4$	74·9	5·0
p-$C_6H_4Pr^n$	,,	Toluene	247—248	75·3	5·3	$C_{21}H_{18}O_4$	75·4	5·4
p-$C_6H_4Bu^n$	,,	Toluene	248—249	75·7	5·8	$C_{22}H_{20}O_4$	76·0	5·8
p-C_6H_4·C_5H_{11}	,,	Toluene	237—238	76·2	6·0	$C_{23}H_{22}O_4$	76·3	6·1
p-C_6H_4·C_6H_{13}	,,	Toluene	229—230	76·4	6·4	$C_{24}H_{24}O_4$	76·6	6·4
p-Tolyl	*p*-Tolyl	Pyridine	288—290	74·8	4·9	$C_{20}H_{16}O_4$	75·0	5·0
p-C_6H_4Et	,,	Pyridine	258—259	75·6	5·3	$C_{21}H_{18}O_4$	75·4	5·4
p-$C_6H_4Pr^n$	,,	Toluene	227—229	75·8	5·7	$C_{22}H_{20}O_4$	76·0	5·8
p-$C_6H_4Bu^n$	,,	Toluene	208—210	76·2	6·0	$C_{23}H_{22}O_4$	76·3	6·1
p-C_6H_4·OMe	Ph	Pyridine	267—269	70·4	4·4	$C_{19}H_{14}O_5$	70·8	4·4
p-C_6H_4·OEt	,,	Toluene	254—256	71·2	4·6	$C_{20}H_{16}O_5$	71·4	4·8
p-C_6H_4·OPr^n	,,	Toluene	259—261	71·9	5·1	$C_{21}H_{18}O_5$	72·0	5·2
p-C_6H_4·OBu^n	,,	Dioxan	257—258	72·6	5·3	$C_{22}H_{20}O_5$	72·5	5·5
p-C_6H_4·OC_5H_{11}	,,	Dioxan	257—258	72·9	5·7	$C_{23}H_{22}O_5$	73·0	5·9
p-C_6H_4·OC_6H_{13}	,,	Dioxan	249—251	73·4	6·3	$C_{24}H_{24}O_5$	73·5	6·2
Pr^n	,,	Dioxan	232—234	69·5	5·6	$C_{15}H_{14}O_4$	69·8	5·5
Bu^n	,,	Dioxan	309—310	70·2	5·8	$C_{16}H_{16}O_4$	70·4	5·9
C_5H_{11}	,,	Toluene	268—270	71·5	6·3	$C_{17}H_{18}O_9$	71·3	6·3
C_6H_{13}	,,	Dioxan	234—236	71·9	6·5	$C_{18}H_{20}O_4$	72·0	6·7
C_7H_{15}	,,	Toluene	232—233	72·6	7·1	$C_{19}H_{22}O_4$	72·6	7·05
C_8H_{17}	,,	Dioxan	184—186	73·2	7·2	$C_{20}H_{24}O_4$	73·1	7·4
Ph	Ph·$[CH_2]_2$	Dioxan	193—195	74·9	5·1	$C_{20}H_{16}O_4$	75·0	5·0
,,	Ph·$[CH_2]_3$	Dioxan	294—296	75·2	5·4	$C_{21}H_{18}O_4$	75·4	5·4
,,	Ph·$[CH_2]_4$	Dioxan	232—234	75·9	5·7	$C_{22}H_{20}O_4$	75·8	5·8

* First purified through the sparingly soluble Na salt. † With decomp. ‡ Atromentin dimethyl ether; Agaki (*J. Pharm. Soc. Japan*, 1942, **62**, 191) gives m. p. 295—297°. § With 2 mols. of pyridine of crystallization. ** Found: Cl, 10·3. Reqd.: Cl 10·4%. †† Found: Br, 20·4. Reqd.: Br, 20·7%. ‡‡ Found: Cl, 19·4. Reqd.: Cl, 19·1%. ‖ Found: Br, 26·8%. Reqd.: Br, 26·3%.

ethanol (500 ml.). The residue (7·5 g.) was crude 2,5-*dichloro*-2,5-*di*-4′-*methylphenyl*-3,6-*di*-p-*tolyl*-1,4-*benzoquinone* (see Table). The extracts, on cooling, deposited the *monoarylbenzoquinone* which was crystallized once from aqueous ethanol and once from acetic acid, the pure product (22·5 g.) forming orange needles, m. p. 146—147° (Found: C, 58·3; H, 3·0; Cl, 26·2. $C_{13}H_8Cl_2O_2$ requires C, 58·4; H, 3·0; Cl, 26·6%).

3,6-*Dichloro*-2-*phenethyl*-5-*phenyl*-1,4-*benzoquinone*.—The following outlines the procedure used in the peroxide alkylation method. A freshly prepared and standardized [3] ether solution of β-phenylpropionyl peroxide (1 mol.) was introduced below the surface of a solution of 3,6-dichloro-2-phenyl-1,4-benzoquinone (5 g.) in acetic acid (50 ml.) so that the temperature remained at 90—95°. Heating was continued for ½ hr. after visible gas evolution ceased. After removal of the solvent and crystallization from ethanol, yellow needles (5·9 g.) of the *quinone*, m. p. 94—96°, were obtained (Found: C, 67·1; H, 3·8; Cl, 19·8. $C_{20}H_{14}Cl_2O_2$ requires C, 67·2; H, 3·9; Cl, 19·8%). Hydrolysis with sodium hydroxide by the described method [1] gave the *dihydroxy-quinone* (5·2 g.) (see Table). Repetition of the synthesis without intermediate purification of the dichloroquinone gave the dihydroxyquinone (6·3 g.) after hydrolysis and crystallization.

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