(66%); uv_{max} (H_2O) 275 (pH 7), 295, 315 nm (shoulder) (pH 13); ν_{max} (KBr) 1660 (C=C), 3350 cm^{-1} (OH). *Anal.* ($C_9H_7F_3O$) C, H.

1-**Trifluoromethyl-2-(4-hydroxyphenyl)ethane (4).** A solution of 0.04 g of **3** (0.21 mmol) in 4 ml of absolute EtOH was hydrogenated at room temperature at 1 atm in the presence of 0.01 g of 10% Pd/C. Reduction was complete in 10 min and filtration of the catalyst and removal of solvent gave a quantitative yield of product as a clear oil. The oil was distilled at 75° (bath temperature) and 0.1 mm to give a product which showed no C=C band in the ir; uv_{max} (H_2O) 272 (pH 7), 292 nm (pH 13). *Anal.* ($C_9H_9F_3O$) C, H.

Product Analysis. The phenol (0.05 g) was dissolved in 0.5 ml of 1 *N* NaOH and the solution allowed to stand at room temperature for 12 hr. Uv spectra in base at this time corresponded to those reported for the corresponding hydroxy acids.[24-26] The solutions from **1** and **2** were acidified to pH 1-2 with concentrated HCl and cooled to give crystals. **1** gave salicylic acid, 0.02 g, mp 155-157°; **2** gave *p*-hydroxybenzoic acid, 0.03, g, mp 213-214°. Hydrolyzed **3** was acidified with Dowex 50-X8 (H^- form) to give *p*-coumaric acid, 0.01 g, mp 210-215°; ir spectrum identical with literature spectrum.[27]

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References

(1) D. V. Santi and T. T. Sakai, *Biochemistry*, **10**, 3598 (1971).
(2) C. Heidelberger, L. Griesbach, B. Montag, D. Mooren, O. Cruz, R. Schnitzer, and E. Grunberg, *Cancer Res.*, **18**, 305 (1958).
(3) F. Pattison and R. Peters in "Handbuch der experimentellen Pharmakologie," Vol. XX, Springer-Verlag, New York, N. Y., 1966, p 387.
(4) Reference 3, 2nd ed, 1970, p 256.
(5) P. Goldman, *Science*, **164**, 1123 (1969).
(6) J. D. Roberts, R. L. Webb, and E. A. McElhill, *J. Amer. Chem. Soc.*, **72**, 408 (1950).
(7) R. Filler and H. Novar, *Chem. Ind. (London)*, 1273 (1960).
(8) R. Jones, *J. Amer. Chem. Soc.*, **69**, 2347 (1947).
(9) H. J. Nestler and E. R. Garrett, *J. Pharm. Sci.*, **57**, 1117 (1968).
(10) M. P. Mertes, S. E. Saheb, and D. Miller, *J. Med. Chem.*, **9**, 876 (1966).
(11) D. V. Santi and A. L. Pogolotti, Jr., *J. Heterocycl. Chem.*, **8**, 265 (1971).
(12) W. C. Smith, *Angew. Chem., Int. Ed. Engl.*, **1**, 467 (1962).
(13) R. McDonald and T. Campbell, *J. Org. Chem.*, **24**, 1969 (1959).
(14) M. Buxton, M. Stacey, and J. Tatlow, *J. Chem. Soc.*, 366 (1954).
(15) R. Filler and H. Novar, *J. Org. Chem.*, **26**, 2707 (1961).
(16) E. S. Lane, *Chem. Ind. (London)*, 788 (1953).
(17) S. Cohen and N. Dinar, *J. Amer. Chem. Soc.*, **87**, 3195 (1965).
(18) E. Kun, D. Fanshier, and D. Grassetti, *J. Biol. Chem.*, **235**, 416 (1960).
(19) D. Clark, J. Nicklas, and J. Palumbo, *Arch. Biochem. Biophys.*, **123**, 205 (1968).
(20) P. Reyes and C. Heidelberger, *Mol. Pharmacol.*, **1**, 15 (1965).
(21) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," Methuen, London, 1962, p 16.
(22) T. T. Sakai, A. L. Pogolotti, and D. V. Santi, *J. Heterocycl. Chem.*, **5**, 849 (1968).
(23) A. C. Bratton and E. K. Marshall, *J. Biol. Chem.*, **128**, 537 (1939).
(24) L. Doub and J. Vandenbelt, J. Amer. Chem. Soc., **77**, 4535 (1955).
(25) E. R. Garrett, *ibid.*, **80**, 4049 (1958).
(26) T. Geissmann and B. J. Harborne, *Arch. Biochem. Biophys.*, **55**, 450 (1955).
(27) I. Pearl, *J. Org. Chem.*, **24**, 737 (1959).

Oxidation of Furans. 2.† Synthesis and Biological Properties of 6-Hydroxy-2*H*-pyran-3(6*H*)-ones and Derivatives

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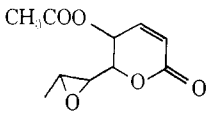
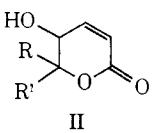
The anticoccidial and *in vitro* antimicrobial properties of a series of 6-hydroxy-2*H*-pyran-3(6*H*)-ones VI and their derivatives VII-XI were investigated. Compounds VI were readily prepared by the peracid oxidation of the appropriate 2-furanmethanols V. Activity was mostly found with compounds substituted with a 4-biphenylyl group and, in particular, **29-47**. The nature of the substituents greatly influenced the degree and type of activity.

In a recent communication,[1] we briefly reported the synthesis of 6-hydroxy-2*H*-pyran-3(6*H*)-ones VI (R^3 = H). These pyran derivatives are chemically related to the naturally occurring antibiotic asperlin I, isolated from *Aspergillus nidulans*,[2] and they were considered to be the most suitable starting materials for the preparation of analogs II of asperlin. Unexpectedly, very good *in vitro* antimicrobial properties were found in compounds of type VI rather than in the analogs II. The present paper will give a more detailed account of the chemistry of 6-hydroxy-2*H*-pyran-3(6*H*)-ones and discuss their biological properties as well as those of their derivatives VII-XI.



I, asperlin



II

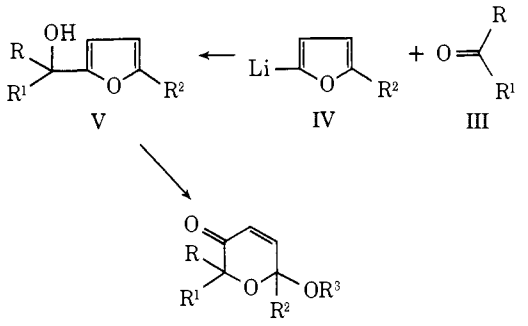
† For part 1, see ref 1.

Chemistry. 1. 6-Hydroxy-2*H*-pyran-3(6*H*)-ones VI (R^3 = H). As previously reported, [1] the hydroxypyranones VI (R^3 = H) were prepared by the process depicted in Scheme I; reaction of an aldehyde or ketone III with a furyllithium derivative IV afforded the 2-furanmethanols V which were converted into VI upon treatment with *m*-chloroperbenzoic acid (or occasionally peracetic acid) in chloroform or methylene chloride. Exceptionally the furanmethanol XIII, precursor of compound **65** (Table I), was prepared by reacting the lithium derivatives XII with 2-acetylfuran (Scheme II). In view of their unstability the 2-furanmethanols were used without purification.

2. Derivatives of 6-Hydroxy-2*H*-pyran-3(6*H*)-ones (VII-XI). Most 6-hydroxy-2*H*-pyran-3(6*H*)-ones were found to be sensitive to strong acid or alkaline media‡ and special precautions had to be taken for the preparation of the derivatives VII-XI.

‡In strongly acidic media the 6-hydroxy-2*H*-pyran-3(6*H*)-ones are converted into crotonic acid γ-lactone derivatives, while they dimerize in alkaline media.

Scheme I



VI, R^3 = H
VII, R^3 = acyl
VIII, R^3 = alkyl or tetrahydropyranyl
IX, R^3 = monoalkylcarbamoyl
X, R^3 = dialkylcarbamoyl
XI, R^3 = alkyl carbonate or alkyl thiocarbonate

R, R^1 are H, alkyl, or aryl
R^2 is in general H; occasionally alkyl or aryl

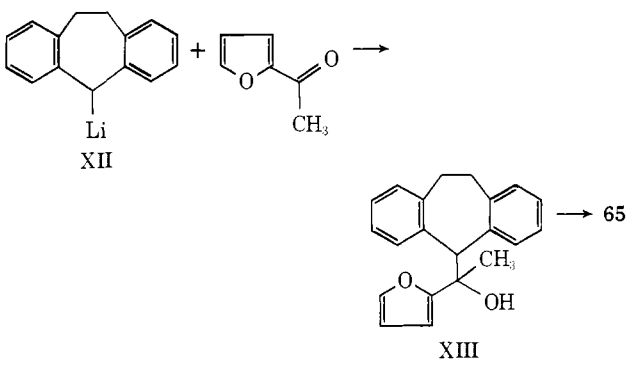
The esters VII were obtained by treating VI (R^3 = H) with acyl anhydrides, preferably in the presence of sodium acetate. In the same manner compounds VI were converted to the corresponding carbamates IX and carbonates or thiocarbonates XI upon reaction with the appropriate isocyanates and chloroformates or chlorothioformates in the presence of triethylamine. Replacing the above reagents with dialkylcarbamoyl chloride yielded the dialkylcarbamates X but only under specific experimental conditions.

Unexpectedly, the 6-hydroxy-2*H*-pyran-3(6*H*)-ones VI (R^2 = R^3 = H) could not be converted to the methyl ethers with methanol and a strong acid, in contrast to the analogous reaction in carbohydrate chemistry. They were formed with methyl iodide and silver oxide. When R^2 was alkyl, however, the methyl ethers could be obtained with methanol and *p*-toluenesulfonic acid. The higher ether homologs were synthesized by reacting a methylcarbamate IX (R^3 = $CONHCH_3$) with the appropriate primary or secondary alcohols in the presence of acid. This method allowed the detection of two isomers, arbitrarily designated as A and B. Isomer A was predominantly obtained by classical methods while isomer B was predominant in the exchange method. Reaction of the carbamate **43** with acetic acid and acid similarly gave the acetates **30** and **31**. In this case, however, isomer A (**30**) was predominant. The relative configuration of the two isomers was not established. The 6-hydroxy-2*H*-pyran-3(6*H*)-ones and their derivatives are listed in Tables I and II.

Biology. 1. Methods. (a) Antibacterial Screening. The compounds were tested *in vitro* against a variety of bacteria by halving dilutions in nutrient broth (Difco). The gram-positive organisms were *Staphylococcus pyogenes* S (penicillin-sensitive), *Staphylococcus pyogenes* R (penicillin-resistant), and *Streptococcus faecalis*. The gram-negative organisms were *Escherichia coli* No. 198, *Aerobacter aerogenes*, *Salmonella pullorum*, *Pseudomonas aeruginosa*, *Proteus vulgaris*, *Klebsiella pneumoniae*, and *Serretia marcescens*. The results are expressed in Tables I and II as the minimum concentration of the compound which inhibits growth after 24 hr of incubation at 37°.

(b) Antifungal Screening. The compounds were screened *in vitro* against a yeast and fungi by halving dilutions in Sabouraud broth. The organisms were *Candida albicans*, *Microsporum gypseum*, and *Trichophyton granulosum*. The results are expressed as the minimum concentration of the compound which inhibits growth after 5 days of incubation at 37° for *Candida albicans* and 10 days at 28° for the two other organisms.

Scheme II



In these two screens, compounds that inhibit growth at a concentration greater than 32 μg/ml are designated as being inactive (−).

(c) Anticoccidial Screening. The compounds were screened for their anticoccidial properties against *Eimeria tenella* in experimental infections in chickens. The test compounds were administered orally 1 day prior to infection at a concentration of 0.05% of the diet. The efficacy was evaluated after 6 days on the basis of survival and weight gains. In Tables I and II the compounds are designated as *inactive* (−) when survival and weight gains are equal to or poorer than the nonmedicated infected controls, *slightly active* (+) when there is improved weight gains but little improvement in mortality, *active* (++) when there is moderate improvement in both parameters, and *very active* (+++) when weight gains and survival are equal to that of the noninfected controls.

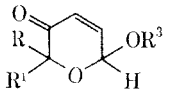
2. Results. Two general observations may be drawn from Tables I and II. First, antimicrobial and anticoccidial activities were mainly found with compounds substituted with a biphenylyl residue or by a similar group (dibenzofuryl or 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptadienyl). Second, minor chemical modifications often produced unpredicted effects on activity. This is particularly the case for compounds **29–47** where the nature of R^3 had influence both on the degree and the type of activity.

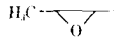
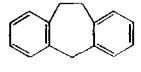
(a) Antibacterial Activity. As a rule the 6-hydroxy-2*H*-pyran-3(6*H*)-ones and their derivatives only exhibited activity against gram-positive bacteria and were essentially inactive against gram-negative organisms. Derivatives, particularly ethers, were the most effective compounds. Worth mentioning are the ethers **37–39** and the heptanoate **13**. Carbamates were generally inactive. With the exception of **51**, **63**, and **65** compounds in Table I in which R^2 = R^3 = H were found to exhibit little activity. Replacement, however, of the hydrogen in position 6 by an alkyl group (Table II, $R^2 \neq$ H) produced an enhancement of activity.

(b) Antifungal Activity. Antifungal activity was mostly found against *Microsporum gypseum* and *Trichophyton granulosum*, while little activity was noted against *Candida albicans* with the exception of **6** and **39**. Contrary to the antibacterial effects, activity was found with the 6-hydroxy-2*H*-pyran-3(6*H*)-ones as well as with their derivatives. Compounds **11**, **12**, **16**, **28**, **30**, **33**, **39**, **41**, **57**, and **58** were highly active.

(c) Anticoccidial Activity. The most effective agents were the carbamate derivatives, particularly **25**, **43**, **44**, **53**, and **66**. Also worth mentioning is the ether **39**. Effectiveness was demonstrated at a dose of 0.05% of the diet

Table I. 6-Hydroxy-2*H*-pyran-3(6*H*)-ones and Derivatives. Structures and Activity

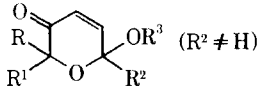


Compd no.	R	R^1	R^3	Formula	Yield, %	Mp, °C	Solvents[a]	Antimicrobial activity (*in vitro*), MIC values in μg/ml						
								Staph. pyogenes S	*Staph. pyogenes* R	*Strep. faecalis*	*C. albicans*	*M. gypseum*	*T. granulosum*	Anticoccidial
1	H	H	H	$C_5H_6O_3$[b]	41	58–59	E–H	—[g]	—	—	—	—	—	—
2		H	H	$C_8H_{10}O_4$[c]		Oil		—	—	—	—	—	—	—
3	$C_6H_5CH(CH_3)$	H	H	$C_{13}H_{14}O_3$	40	84–85	E–H	—	—	—	—	—	32	—
4	C_6H_5	H	H	$C_{11}H_{10}O_3$	70	74–75	E–H	—	—	—	—	—	32	—
5	C_6H_5	H	CH_3CO	$C_{13}H_{12}O_4$	40	64–65	E–H	—	—	—	—	32	4	ND[h]
6	*p*-$C_6H_5CH_2OC_6H_4$	H	H	$C_{18}H_{16}O_4$	55	92–94	E–H	—	—	—	3.2	4	8	—
7	*p*-$C_6H_5CH_2OC_6H_4$	H	CH_3CO	$C_{20}H_{18}O_5$	70	118–119	T–H	—	—	—	—	4	4	—
8	*p*-ClC_6H_4	H	H	$C_{11}H_9ClO_3$	68	93–95	M	—	—	—	—	—	8	—
9	2,4-$Cl_2C_6H_3$	H	H	$C_{11}H_8Cl_2O_3$	37	146–147	B	12.5	12.5	12.5	—	—	16	—
10	*p*-$C_6H_5C_6H_4$	H	H	$C_{17}H_{14}O_3$	75	124–126	B	—	—	—	16	8	4	—
11	*p*-$C_6H_5C_6H_4$	H	CH_3CO	$C_{19}H_{16}O_4$	80	96–98	E	—	—	—	16	4	2	+
12	*p*-$C_6H_5C_6H_4$	H	$CH_3(CH_2)_2CO$	$C_{21}H_{20}O_4$	62	73–74	M	—	—	—	—	2	2	—
13	*p*-$C_6H_5C_6H_4$	H	$CH_3(CH_2)_3CO$	$C_{24}H_{26}O_4$	72	<room temp		1.6	3.2	1.6	—	32	16	ND
14	*p*-$C_6H_5C_6H_4$	H	$ClCH_2CO$	$C_{19}H_{15}ClO_4$	75	69–71	T	—	—	—	16	4	4	—
15	*p*-$C_6H_5C_6H_4$	H	2-Tetrahydropyranyl	$C_{22}H_{22}O_4$	60	80–83	H	6.2	6.2	6.2	—	32	32	—
16	*p*-$C_6H_5C_6H_4$	H	CH_3	$C_{18}H_{16}O_3$	60	69–71	M	6.2	3.2	6.2	16	4	2	—
17	$(C_6H_5)_2CH$	H	H	$C_{18}H_{16}O_3$	62	159–160	B	—	—	—	—	—	—	+
18	$(C_6H_5)_2CH$	H	C_2H_5OCO	$C_{21}H_{20}O_5$	65	76–77	E–H	—	—	—	—	—	—	+
19	2-Dibenzofuryl	H	H	$C_{17}H_{12}O_4$	50	117–118	T	—	—	—	16	1	8	—
20		H	H	$C_{20}H_{18}O_3$[d]	85	150–152	M	—	—	—	—	32	16	+
21	5′-$C_{15}H_{13}$	H	CH_3OCO (A)	$C_{22}H_{20}O_5$	85	148–150	E	—	—	—	—	—	—	+
22	5′-$C_{15}H_{13}$	H	CH_3	$C_{21}H_{20}O_3$	80	107–108	M	3.2	6.2	2.5	—	16	4	—
23	C_6H_5	CH_3	H	$C_{12}H_{12}O_3$		81–82.5	A–H	—	—	—	—	—	—	ND
24	$(C_6H_5)_2CH$	CH_3	H	$C_{19}H_{18}O_3$	75	141–142	A–H	25	12.5	25	—	—	—	ND
25	$(C_6H_5)_2CH$	CH_3	CH_3NHCO	$C_{21}H_{21}NO_4$		82–84	E	—	—	—	—	—	—	++
26	3,4-$(CH_3)_2C_6H_3$	C_6H_5	H	$C_{19}H_{18}O_3$[d]	55	158–160	M	12.5	12.5	12.5	ND	32	32	—
27	3,4-$(CH_3)_2C_6H_3$	C_6H_5	CH_3CO	$C_{21}H_{20}O_4$	70	Oil		3.2	3.2	1.6	—	—	—	ND
28	*p*-$C_6H_5C_6H_4CH_2$	CH_3	H	$C_{19}H_{18}O_3$	75	115–116	E–H	—	—	—	—	4	0.5	—
29	*p*-$C_6H_5C_6H_4$	CH_3	H	$C_{18}H_{16}O_3$	80	166–167	M	12.5	12.5	25	—	—	—	—
30	*p*-$C_6H_5C_6H_4$	CH_3	CH_3CO (A)	$C_{20}H_{18}O_4$	60	89–90	E	12.5	25	12.5	—	4	0.8	+
31	*p*-$C_6H_5C_6H_4$	CH_3	CH_3CO (B)	$C_{20}H_{18}O_4$	20	103–105	H	3.2	6.2	6.2	16	4	2.5	ND
32	*p*-$C_6H_5C_6H_4$	CH_3	*p*-$NO_2C_6H_4CO$	$C_{25}H_{19}NO_5$	20	130–131	C	3.2	6.2	3.2	—	—	—	+
33	*p*-$C_6H_5C_6H_4$	CH_3	CH_3 (A)	$C_{19}H_{18}O_3$	70	85–87	E H	6.2	6.2	6.2	32	2	0.8	+
34	*p*-$C_6H_5C_6H_4$	CH_3	CH_3 (B)	$C_{19}H_{18}O_3$	70	68–70	H	6.2	6.2	12.5	16	2	8	—
35	*p*-$C_6H_5C_6H_4$	CH_3	C_2H_5 (B)	$C_{20}H_{20}O_3$	80	90–92	H	6.2	6.2	6.2	—	—	—	—
36	*p*-$C_6H_5C_6H_4$	CH_3	$(CH_3)_2CH$ (A)	$C_{21}H_{22}O_3$	80	62–64	PE_{30}	6.2	6.2	6.2	—	—	—	ND
37	*p*-$C_6H_5C_6H_4$	CH_3	$(CH_3)_2CH$ (B)	$C_{21}H_{22}O_3$	80	80–82	PE_{30}	1.6	1.6	1.6	32	—	—	—
38	*p*-$C_6H_5C_6H_4$	CH_3	$C_6H_5CH_2$ (B)	$C_{25}H_{22}O_3$	65	95–97	H	0.8	0.8	0.8	—	—	—	—
39	*p*-$C_6H_5C_6H_4$	CH_3	$CH_3O(CH_2)_2$ (A)	$C_{21}H_{22}O_4$	5	67–69	H	0.8	6.2	6.2	4	4	1.2	++
40	*p*-$C_6H_5C_6H_4$	CH_3	CH_3OCO	$C_{20}H_{18}O_5$	83	104–106	E	—	—	—	ND	ND	ND	+
41	*p*-$C_6H_5C_6H_4$	CH_3	C_2H_5OCO	$C_{21}H_{20}O_5$	85	58–60	E–H	—	—	—	—	—	0.2	+
42	*p*-$C_6H_5C_6H_4$	CH_3	C_2H_5SCO	$C_{21}H_{20}O_4S$	75	75–77	H	—	—	—	32	8	8	—

43	p-$C_6H_5C_6H_4$	CH_3	CH_3NHCO	$C_{20}H_{19}NO_4$	82	127–128	A–H	—	—	—	—	16	16	++
44	*p*-$C_6H_5C_6H_4$	CH_3	$(CH_3)_2NCO$	$C_{21}H_{21}NO_4$	65	120–122	E	6.2	6.2	6.2	—	8	—	+++
45	*p*-$C_6H_5C_6H_4$	CH_3	C_2H_5NHCO	$C_{21}H_{21}NO_4$	85	90-92	PE_{60}	—	—	—	—	8	4	+
46	*p*-$C_6H_5C_6H_4$	CH_3	$(C_2H_5)_2NCO$	$C_{23}H_{25}NO_4$	40	116–117	E	—	—	—	—	—	—	+
47	*p*-$C_6H_5C_6H_4$	CH_3	*n*-C_3H_7NHCO	$C_{22}H_{23}NO_4$	80	100–101	B	—	—	—	—	8	8	—
48	*p*-$ClC_6H_4C_6H_4$	CH_3	H	$C_{18}H_{15}ClO_3$	76	159–160	B	6.2	6.2	6.2	32	2	8	+
49	*p*-$ClC_6H_4C_6H_4$	CH_3	CH_3CO	$C_{20}H_{17}ClO_4$	84	80-81	H	3.2	3.2	3.2	ND	ND	ND	—
50	*p*-$ClC_6H_4C_6H_4$	CH_3	CH_3NHCO	$C_{20}H_{18}ClNO_4$	90	151–152	A–H	—	—	—	—	16	4	+
51	*p*-$BrC_6H_4C_6H_4$	CH_3	H	$C_{18}H_{15}BrO_3$	85	165–166	A–H	3.2	3.2	6.2	32	0.6	—	—
52	*p*-$BrC_6H_4C_6H_4$	CH_3	CH_3NHCO	$C_{20}H_{18}BrNO_4$	95	155–156	E–H	—	—	—	—	8	16	—
53	*p*-$CH_3OC_6H_4C_6H_4$	CH_3	H	$C_{19}H_{18}O_4$	70	198–199	Et	6.2	12.5	—	—	8	8	—
54	*p*-$C_6H_5C_6H_4$	CH_2Cl	H	$C_{18}H_{15}ClO_3$	85	187-188	N	25	—	—	—	—	—	—
55	*p*-$C_6H_5C_6H_4$	CH_2Cl	CH_3	$C_{19}H_{17}ClO_3$	65	90–92	E–H	1.6	0.8	1.6	—	2	4	—
56	*p*-$C_6H_5C_6H_4$	C_2H_5	H	$C_{19}H_{18}O_3$	75	159–160	A–H	12.5	12.5	12.5	—	—	—	—
57	*p*-$C_6H_5C_6H_4$	C_2H_5	CH_3CO	$C_{21}H_{20}O_4$	90	95- 96	A–H	—	—	—	—	2	2	—
58	*p*-$C_6H_5C_6H_4$	C_2H_5	CH_3NHCO	$C_{21}H_{21}NO_4$	50	123–124	Et–H	—	—	—	—	2	2	+++
59	*p*-$C_6H_5C_6H_4$	C_2H_5	$(CH_3)_2NCO$	$C_{22}H_{23}NO_4$	45	129–130	E	—	—	—	—	—	4	+
60	*p*-$C_6H_5C_6H_4$	*n*-C_3H_7	H	$C_{20}H_{20}O_3$	70	146–147	A–H	—	—	—	32	4	4	+
61	*p*-$C_6H_5C_6H_4$	*n*-C_3H_7	CH_3CO	$C_{22}H_{22}O_4$	70	96–97	E	3.2	3.2	3.2	—	—	8	—
62	*p*-$C_6H_5C_6H_4$	*n*-C_3H_7	CH_3NHCO	$C_{22}H_{23}NO_4$	60	108–110	Et–H	25	25	25	—	4	4	—
63	*p*-$C_6H_5C_6H_4$	C_6H_5	H	$C_{23}H_{18}O_3$	60	137-138	B	3.2	6.2	3.2	—	8	8	—
64	2-Dibenzofuryl	CH_3	H	$C_{18}H_{14}O_4$	57	139–140	T	25	25	25	32	1	4	—
65	5′-$C_{15}H_{13}$	CH_3	H	$C_{21}H_{20}O_3$[d]	60	162–164	B	3.2	3.2	12.5	—	—	—	+
66	5′-$C_{15}H_{13}$	CH_3	CH_3NHCO	$C_{23}H_{23}NO_4$	75	175–178	E	—	—	—	—	—	—	++
Chlorhexidine diacetate								0.8	1.6	3.2	—	—	—	
Griseofulvin											>10	1.25	1.25	
Methyl benzoquate[f]														+++

[a] The recrystallization solvents are A = Me_2CO; B = C_6H_6; C = cyclohexane; E = Et_2O; Et = EtOAc; H = *n*-hexane; M = methylcyclohexane; N = CH_3NO_2; PE_{30} = petroleum ether (bp 30–60°); PE_{60} = petroleum ether (bp 60–90°); T = $C_6H_5CH_3$. [b] This product is highly soluble in H_2O and the work-up is different: at the end of the reaction, the mixture is evaporated to dryness. H_2O is added and the *m*-chlorobenzoic acid is filtered off. The product is isolated by continuous Et_2O extraction. [c] The starting material is crotonaldehyde. The formation of the epoxide is concomitant to that of the pyran ring. [d] The oxidant is 40% peracetic acid in acetic acid. [e] This will be designated by the radical 5′-$C_{15}H_{13}$ in subsequent appearance in the table. [f] Against *Eimeria tenella* at a concentration of 0.002% of the diet. [g] (—) indicates that compounds exhibit MIC > 32 μg/ml and that they are considered inactive. [h] Not determined.

Table II. 6-Hydroxy-2*H*-pyran-3(6*H*)-ones and Derivatives. Structures and Activity



Compd no.	R	R^1	R^2	R^3	Formula	Yield, %	Mp, °C	Solvents[a]	Antimicrobial activity (*in vitro*), MIC values in μg/ml: *Staph. pyogenes* S	*Staph. pyogenes* R	*Strep. faecalis*	*C. albicans*	*M. gypseum*	*T. granulosum*	Anticoccidial
67	*p*-$C_6H_5C_6H_4$	H	CH_3	H	$C_{18}H_{16}O_3$	33	110–111	T–C	6.2	12.5	6.2	—	8	4	—
68	$(C_6H_5)_2CH$	H	CH_3	H	$C_{19}H_{18}O_3$	50	155–156	T	3.2	3.2	3.2	32	—	—	—
69	$(C_6H_5)_2CH$	H	C_2H_5	H	$C_{20}H_{20}O_3$	57	106–107	T	3.2	3.2	12.5	—	—	—	—
70	$(C_6H_5)_2CH$	H	C_2H_5	CH_3	$C_{21}H_{22}O_3$	44	73–74.5	H	—	—	—	—	—	—	—
71	$(C_6H_5)_2CH$	CH_3	CH_3	H	$C_{20}H_{20}O_3$	80	125–126	E–H	3.2	2	6.2	—	—	—	—
72	*p*-$C_6H_5C_6H_4$	C_6H_5	CH_3	H	$C_{24}H_{20}O_3$	40	149–150	A–H	0.8	1.6	0.8	—	32	—	—

[a] The recrystallization solvents are A = Me_2CO; C = cyclohexane; H = *n*-hexane; and T = $C_6H_5CH_3$.

but at lower concentration only marginal activity was detected.

Conclusion

In conclusion, 2-substituted 6-hydroxy-2*H*-pyran-3(6*H*)-ones were found to possess good *in vitro* antimicrobial activities comparable to standard agents. Chemical modifications have led to compounds exhibiting interesting *in vivo* anticoccidial effects.

Experimental Section

The compounds had satisfactory analyses for C and H and where applicable for N, Cl, Br, and S. In addition, the nmr and ir spectra were in agreement with the proposed structures. The melting points are uncorrected.

Starting Materials III. Commercial aldehydes and ketones were used without prior purification. The other starting materials were prepared according to known procedures: 4′-(*p*-chlorophenyl)-, 4′-(*p*-bromophenyl)-, and 4′-(*p*-methoxyphenyl)acetophenones, 4′-phenylpropiophenone, 4′-phenylbutyrophenone, 2-acetyldibenzofuran, and 2-dibenzofurancarboxaldehyde by Friedel-Crafts synthesis[3]; 4-biphenylylacetone from 4-biphenylylacetonitrile by the procedure used for the synthesis of phenylacetone;[4] and 10,11-dihydrodibenzo[*a,d*]cycloheptadiene-5-carboxaldehyde by reacting the corresponding 5-one with methoxymethylmagnesium chloride followed by acid treatment.§

2-Furanmethanols (V). The 2-furanmethanols were obtained from the appropriate carbonyl-containing starting materials III and 2-furyllithium derivatives IV according to a modified method of Ramanathan and Levine.[5]

The furyllithium derivatives were prepared *in situ* by reacting *n*-BuLi with furan, 2-methylfuran, 2-ethylfuran,[6] or 2-phenylfuran.[7] This reaction was carried out in Et_2O at room temperature with furan and preferably in boiling Et_2O for the substituted furans. Freshly prepared (in Et_2O) or commercial (22% in hexane) *n*-BuLi was used.

The general procedure for the preparation of the 2-furanmethanols is illustrated by the following example. Freshly prepared *n*-BuLi in Et_2O (1.88 *N*, 60 ml) was added to a solution of distilled furan (8 ml) in Et_2O (80 ml) cooled to 10°. After stirring for 1 hr at room temperature, 4′-phenylacetophenone (19.6 g, 0.1 mol) was added portionwise. The reaction was allowed to proceed at room temperature for 2.5 hr. The excess furyllithium was decomposed with 50% THF-H_2O, followed by H_2O. The organic layer was washed to neutrality (H_2O), dried ($MgSO_4$), and evaporated, affording crude α-(4-biphenylyl)-α-methyl-2-furanmethanol (23 g, 87%) of sufficient purity for further conversion.

6-Hydroxy-2*H*-pyran-3(6*H*)-ones (VI). The following example will illustrate the general procedure. *m*-Chloroperbenzoic acid (87%, 15.0 g, 0.075 mol) was added by portions to a cold solution of α-(4-biphenylyl)-α-methyl-2-furanmethanol (13.2 g, 0.05 mol), prepared above, in $CHCl_3$ (200 ml). The temperature was kept between 10 and 15° during the addition. After stirring for 90 min at room temperature, the mixture was cooled to 0° and the solid that had formed was filtered (*m*-chlorobenzoic acid). The filtrate was washed (20% KI, 30% $Na_2S_2O_3$, $NaHCO_3$, and H_2O) dried ($MgSO_4$), and concentrated to one-third its volume. Addition of hexane afforded a solid which was stirred for 15 min with methylcyclohexane to give pure **29** (11.2 g, 80%).

In some cases the 6-hydroxy-2*H*-pyran-3(6*H*)-one coprecipitated with *m*-chlorobenzoic acid. This was overcome by using a larger quantity of solvent or 40% peracetic acid as oxidant.

Derivatives of 6-Hydroxy-2*H*-pyran-3(6*H*)-ones (VII-XI). The preparation of the derivatives of **29** will illustrate the general procedures.

Esters VII. Acetate 30. A mixture of **29** (8.0 g, 0.028 mol), Ac_2O (30 ml), anhydrous NaOAc (7.0 g), and C_6H_6 (200 ml) was refluxed for 30 min. The cool mixture was washed (H_2O) and then stirred for 30 min with aqueous $NaHCO_3$. After washing (H_2O) to neutrality, the solution was dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel. Elution with 50% Et_2O-hexane gave an oil which was crystallized from Et_2O to give pure **30** (5.5 g, 60%).

Ethers VIII (Isomer A). Methyl Ether 33. To a solution of **29** (8.0 g, 0.028 mol) in Me_2CO (400 ml) were added with constant stirring MeI (14.2 g, 0.1 mol) and Ag_2O (18.5 g, 0.08 mol). The mixture was stirred at room temperature overnight and filtered on Celite, and the filtrate was evaporated to dryness. The residue was chromatographed on silica gel (ratio 1:100). The pure fractions (tlc system 25% Et_2O-hexane), eluted with 40% hexane-Et_2O, were combined and crystallized from Et_2O-hexane. Recrystallization from hexane gave pure **33** (5.88 g, 70%).

Carbamates IX. Methylcarbamate 43. A solution of **29** (8.0 g, 0.028 mol), MeNCO (4 ml), and Et_3N (5 ml) in C_6H_6 (100 ml) was stirred for 45 min at room temperature. The solution was left at room temperature on a rotating evaporator for 30 min and then washed (H_2O) to neutrality. The dried solution was absorbed on silica gel (ratio 1:15). Elution with 50% Et_2O-hexane gave a solid which was recrystallized from Me_2CO-hexane to yield the methylcarbamate **43** (7.2 g, 82%).

The carbamates are easily cyclized to the corresponding pyranooxazoles. To avoid this, the reaction and isolation of the products must be carried out under mild conditions.

Carbamates X. Dimethylcarbamate 44. 2-(4-Biphenylyl)-6-hydroxy-2-methyl-2*H*-pyran-3(6*H*)-one (**29**, 50.4 g, 0.18 mol) was added to a suspension of NaH dispersed in oil (12 g, 0.5 mol) in C_6H_6 (120 ml); the mixture was stirred under N_2 for 1 hr at room temperature and for 20 min at 30–35°. Me_2NCOCl (30.1 g, 0.28 mol) was slowly added at 30°, giving a mild exothermic reaction (t <40°). The resulting brown solution was kept at 30° for 20 min. After cooling to 10° glacial AcOH (20 ml) was slowly added. The solid that formed was filtered off on Celite and the filtrate was chromatographed on silica gel (ratio 1:40). Elution with 5% EtOAc-C_6H_6 gave an amorphous product which was crystallized from Et_2O. Recrystallization from CH_2Cl_2-hexane gave pure **44** (41 g, 65%).

Carbonates and Thiocarbonates XI. Methyl Carbonate 40. MeOCOCl (11.3 g, 0.12 mol) was slowly added to a cold suspension of **29** (19.6 g, 0.07 mol), Et_3N (12 ml), and CH_2Cl_2 (300 ml). During the addition the temperature was kept at 10°. The mixture was stirred at 20° for 25 min, washed (H_2O), dried ($MgSO_4$), and evaporated. The residual red oil was chromatographed on silica gel (ratio 1:50). Elution with 20% Et_2O-hexane gave a yellow oil which was crystallized from Et_2O. Pure **40** was obtained by further crystallization from Me_2CO-hexane (20.0 g, 85%).

Ethyl Thiocarbonate 42. EtSCOCl (9.96 g, 0.08 mol) was added dropwise to a stirred mixture of **29** (16.8 g, 0.06 mol), Et_3N (8 ml), and Et_2O (400 ml). Stirring was continued for 1 hr. The solid that had formed was filtered. The filtrate was diluted with 500 ml of hexane and absorbed on Florisil (ratio 1:75). Elution with hexane and then with 15% Et_2O-hexane gave an oil which was crystallized from hexane to give the thiocarbonate **42** (16.6 g, 75%).

2-(4-Biphenylyl)-6-tetrahydropyranyloxy-2*H*-pyran-3(6*H*)-one (15). A mixture of 2-(4-biphenylyl)-6-hydroxy-2*H*-pyran-3(6*H*)-one (**10**) (2.66 g, 0.01 mol), dihydropyran (3.5 ml), C_6H_6 (100 ml), and TsOH acid (600 mg) was stirred at room temperature for 30 min. The solution was washed (aqueous $NaHCO_3$ and H_2O), dried ($MgSO_4$), and evaporated. The residual yellow oil was crystallized from methylcyclohexane–hexane. Recrystallization from hexane gave pure **15** (2.12 g, 60%).

6-Ethyl-2-diphenylmethyl-6-methoxy-2*H*-pyran-3(6*H*)-one (70). A mixture of 6-ethyl-2-diphenylmethyl-6-hydroxy-2*H*-pyran-3(6*H*)-one (**69**, 10.7 g, 0.034 mol), MeOH (225 ml), and 70% $HClO_4$ (0.1 ml) was stirred for 10 min at room temperature. The solution was poured into a saturated solution of $NaHCO_3$ and the mixture extracted with Et_2O. The ethereal solution was washed (saturated NaCl solution), dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica gel (ratio 1:50). The fractions eluted with 2% EtOAc-C_6H_6 were combined and crystallized from hexane to give the ether **70** (5.0 g, 44%).

2-(10,11-Dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-yl)-6-hydroxy-2-methyl-2*H*-pyran-3(6*H*)-one (65). *n*-BuLi in hexane (22%, 0.05 mol) was added to a cold solution of 10,11-dihydrodibenzo[*a,d*]cycloheptadiene (9.7 g, 0.05 mol) in anhydrous Et_2O (100 ml). The solution was stirred and refluxed for 1 hr. After cooling to 10°, 2-acetylfuran (5.5 g, 0.05 mol) was added dropwise while keeping the temperature between 10 and 15°. The mixture was stirred at that temperature for 90 min; H_2O was added and the organic layer washed to neutrality. The dried solution was diluted with 100 ml of hexane and absorbed on silica gel (ratio 1:30). Elution with 15% Et_2O-hexane afforded the furanmethanol XIII as a yellow oil (6 g). To a cold solution of the latter in $CHCl_3$ (100 ml), 40% peracetic acid (18 ml) was added dropwise. After stirring for 1 hr at room temperature, the solution was washed (H_2O, $NaHCO_3$, KI, $Na_2S_2O_3$, $NaHCO_3$, H_2O), dried ($MgSO_4$), and concentrated. The residue was crystallized from Et_2O. Recrystallization from C_6H_6 gave pure **65** (9.6 g, overall yield 60%).

§M. A. Davis, Ayerst Research Laboratories, personal communication.

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References

(1) Y. Lefebvre, *Tetrahedron Lett.*, 133 (1971).
(2) A. D. Argondelis and J. F. Zieserl, *ibid.*, 1969 (1966).
(3) (a) P. H. Gore in "Friedel-Crafts and Related Reactions," Vol. III, part 1, C. A. Olah, Ed., Interscience, New York, N. Y., 1964, Chapter 31; (b) C. A. Olah, Ed., "Friedel-Crafts and Related Reactions," Vol. 1, Interscience, New York, N. Y., 1963, Chapter 2, p 119.
(4) A. H. Blatt, Ed., "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, pp 391, 487.
(5) V. Ramanathan and R. Levine, *J. Org. Chem.*, **27**, 1216 (1962).
(6) T. Reichtein, *Helv. Chim. Acta*, **13**, 345 (1930).
(7) A. W. Johnson, *J. Chem. Soc.*, 895 (1946).

Relationship between Physical Properties and Antimalarial Activities of 1,4-Naphthoquinones

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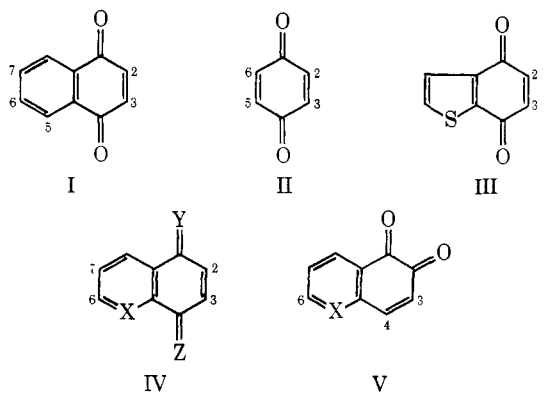
Studies have been made of the lipophilic and oxidation-reduction properties of active *vs.* inactive naphthoquinone antimalarials reported by Fieser in 1948. The results suggest that, in addition to the appropriate partition coefficient, the active quinones possess a rather limited range in ease of reduction as measured by either the energy of the lowest unoccupied molecular orbital (E_{LEMO}) or the redox potential. These results are consistent with the known chemistry and biochemistry of the molecules. The model also correctly predicts the curative properties of 28 series of related molecules (more recently) synthesized as antimalarials.

The relative potency of members of a series of drugs is often considered to be a function of differences in hydrophobic, electronic, and steric factors. In the past several years considerable advances have been made in quantitating such relationships.[1] The ability to anticipate or at least rationalize the boundaries of a series is a related but not identical problem. That is, what factors determine which compounds are members of a set and which apparent analogs will be completely inactive or act by a different mechanism of action? This sort of question implies an all-or-none or threshold type of relationship between a physical property and activity rather than the continuous correlation seen with analogs of varying potency.

The antimalarial naphthoquinones first studied by Fieser, *et al.*,[2] proved to be a very interesting example of this type of problem. In their original analysis of the structure-activity relationships of the 2-alkyl-3-hydroxy-1,4-naphthoquinones, it was shown conclusively that there is a marked dependence of potency on lipophilic character.[3] However, nonoptimum hydrophobic character does not explain the inactivity of the large number of derivatives reported to be inactive[4] (ED_{95} of >400 mg/kg in Table I). We were interested to discover if the compounds are inactive for electronic or for steric reasons.



The naphthoquinones probably exert their antimalarial activity by competing with coenzyme Q to disrupt mitochondrial electron transport.[2,5,6] On the basis of this mechanism of action we expected that the inactive molecules should differ from the active ones in oxidation-reduction properties. As a measure of these properties we calculated (1) the energy of the lowest empty molecular orbital (E_{LEMO}) by the Hückel technique and (2) the standard redox potential, E_0.

Experimental Section

Since the drugs act within the lipoidal mitochondrion, the physical properties were calculated for the uncharged species.

Partition Coefficients (P). The log P values were calculated from known values by additivity procedures.[7] Except where noted π values (log P [derivative] − log P [parent]) were taken from Fujita, *et al.*,[8] for the aromatic ring substituents. The known log P's which were used are listed in Table II. Ring systems other than 1,4-naphthoquinones were calculated as follows.

1,4-Quinolinequinone: the difference between the log P for naphthalene and quinone is 1.34. Therefore, since 1,4-naphthoquinone has a log P of 1.71, the equivalent quinoline would have a log P of 1.71 − 1.34 or 0.37. 1,4-Thionaphthenequinone: this log P was calculated in the same manner as the 1,4-quinolinequinone. The difference between the log P for naphthalene and thionaphthalene is 0.25; therefore, the log P for 1,4-thionaphthenequinone would be 1.71 − 0.25 or 1.46.

Other values can be calculated in the same way. For example, the log P for a 3-isoamyl substitution is the log P for 2-hydroxy-3-isoamyl-1,4-naphthoquinone minus the log P for 2-hydroxy-1,4-naphthoquinone or 3.87 − 1.38 or 2.49. Likewise the log P for a 3-$(CH_2)_3C_6H_{11}$ substituent is 5.31 − 1.38 or 3.93 and for 2-OH is 1.38 − 1.71 or −0.33. Log P values were calculated in this manner for all compounds reported.

It is assumed that 1,4-naphthoquinoneimine has the same log P as 1,4-naphthoquinone, or the imine group has the same contribution to P as the carbonyl group.

Log P's for the 1,2-naphthoquinones were reduced by 1.00 from that of the corresponding 1,4-naphthoquinone. This is based on the measured cyclohexane values reported in ref 7.

E_0. Whenever data were available E_0 values were calculated by summing substituent effects upon E_0 of the parent or related quinone. For example, the substituent effect of a 2-methyl group was