[CONTRIBUTION FROM THE RESEARCH LABORATORIES, METALSALTS CORP.]

Oxine Ester Salicylates as Antifungal Agents[1]

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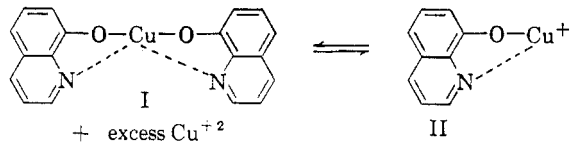
Salts of lipoidal, ionic character were obtained by the selective reactions of 8-quinolinyl benzoate with certain salicylic acids. Other oxine esters were similarly utilized. Several members of the series showed high anti-fungal activity in preliminary *in vitro* screening.

The use of 8-hydroxyquinoline (oxine) and its derivatives as antibacterial and antifungal agents extends over the past sixty years. Esters from carboxylic acids and these phenolic compounds have been synthesized[2-13] in an effort to extend the spectrum of antimicrobial activity as well as to remove undesirable properties attributed in part to the phenolic group such as irritation, sensitization, and toxicity.[14,15] Harper,[16] in discussing the possible means for presenting a potentially useful drug in a stable, nonirritant, relatively nontoxic, acceptable form with the desired activity, includes esterification as a method of drug latentiation.

However, two properties deemed essential for an antifungal agent are that it be lipoidal for the penetration of fungus cell walls and ionic to interact with the cellular enzymes. The lower antimicrobial efficiency of fat-soluble oxine esters reported in the past can be linked to their nonionic nature. Block[17] has demonstrated the importance of these two requirements in a study of the mode of action of oxine and its derivatives. The reversal of its fungitoxicity in the presence of excess metal—e.g., copper—was due to the suppression of the cell penetrating 2:1 oxine copper chelate I to yield the nonlipoidal ionic 1:1 oxine copper chelate II,



which is not taken up by fungus cells. The adverse effect of the presence of excess oxine on its fungitoxicity was attributed to an opposite shift in equilibrium between the two chelate forms within the cell, I thus being favored. This nonionic chelate is nontoxic compared to the intracellular poison II. Similarly, the nonlipoidal oxine cation, $C_9H_7ON^+H$, which forms from oxine and acids at low *p*H, is without activity because it remains outside of the fungus cell. Byrde *et al.*,[17] in a study of the effectiveness of a series of 5-*n*-alkyloxines, also found biophase solubility to be an important requirement for antifungal activity. In order to secure compounds which would possess lipophilic properties as well as ionic character we decided to prepare carboxylic acid salts of carboxylic acid esters of oxine and its derivatives. A search of the literature failed to reveal the synthesis or isolation of such products.

We encountered unexpected difficulty with the simplest aromatic acid ester, 8-quinolinyl benzoate, which was first synthesized by Bedall and Fischer.[18] It failed to form isolatable salts with a variety of acids including citric, maleic, malonic, phthalic, and tartaric acids. In contrast, nonesterified 8-hydroxyquinoline readily yielded the known salts with these acids. Our efforts were equally unsuccessful when polar or non-polar solvent systems were employed. That acid strength was not the criterion for stable salt formation was demonstrated by similar failure with *o*-sulfobenzimide (K_a = 2.5×10^{-2}). The availability of the heterocyclic nitrogen's unshared electron pair, of both esters and ethers of 8-hydroxyquinoline to form quater-

(1) Presented at the F. F. Blicke Symposium, Division of Medicinal Chemistry, American Chemical Society Meeting, New York, N. Y., September 13, 1960.

(2)(a) J. P. Phillips, *Chem. Revs.*, **56**, 280 (1956). (b) C. J. Cavallito and T. H. Haskell, *J. Am. Chem. Soc.*, **66**, 1168 (1944).

(3) H. P. Kaufmann and L. S. Huang, *Ber. deut. chem. Ges.*, **75**, 1217 (1942).

(4) E. Lippman, *Monatsh. Chem.*, **8**, 439 (1887).

(5) E. P. Taylor, *J. Chem. Soc.*, 1311 (1952).

(6) H. Vogt, *Arch. Pharm.*, **282**, 27 (1944).

(7) R. Wolffenstein, Ger. Pat. **281,007**, Dec. 2, 1944.

(8) F. Zetsche, H. Silberman, and G. Vieli, *Helv. Chim. Acta*, **8**, 602 (1925).

(9) J. Altpeter, *Pharm. Zentralhalle*, **70**, 805 (1929).

(10) H. Vogt and P. Jeske, *Arch. Pharm.*, **291**, 168 (1958).

(11) R. Neher, U. S. Patent **2,666,058**, Jan. 12, 1954.

(12) H. Zinner and H. Fiedler, *Arch. Pharm.*, **291**, 330 (1958).

(13) R. Becher, Brit. Patent **791,409**, March 5, 1958.

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(15) W. Leifer and K. Steiner, *J. Invest. Dermatol.*, **17**, 233 (1951).

(16) N. J. Harper, *J. Medicin. Pharm. Chem.*, **1**, 467 (1959).

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(18) K. Bedall and O. Fischer, *Ber. deut. chem. Ges.*, 14, 1366 (1881); K. Matsumura, *J. Am. Chem. Soc.*, **52**, 4433 (1930).

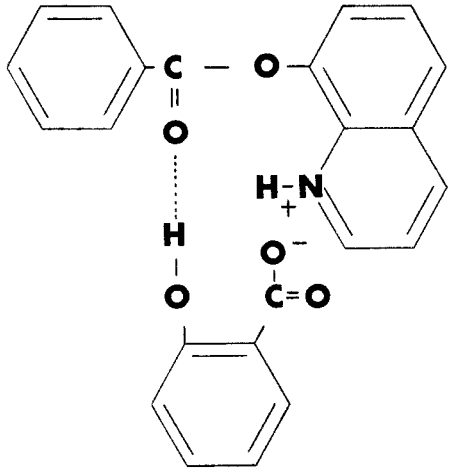

Figure 1

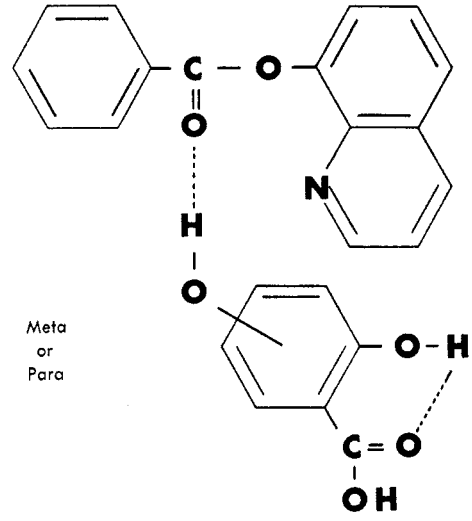

Figure 2

nary salts with such reagents as alkyl halides,[19] and dimethyl sulfate[6,10] has been observed.

Uniquely, salicylic acid formed a well defined salt with 8-quinolinyl benzoate, but no reaction was noted with *m* or *p*-hydroxybenzoic acid. This selectivity may represent a type of co-operative bonding brought about by the formation of a typical ionic salt held in addition by a hydrogen bond between the oxygen of the ester carbonyl and the hydrogen of the *ortho* hydroxyl (Fig. 1). Evidence for the ability of esters of benzoic acid, such as the methyl or ethyl, to participate in hydrogen bond formation by accepting a proton at the O atom of the carbonyl group has been obtained by M. Ito and co-workers.[20] A shift in the ultraviolet absorption spectrum towards the red was noted, the magnitude being determined by the proton donating power of the partner molecule. The isomers of hydroxybenzoic acid differ markedly in hydrogen bond–forming properties; chelate ring formation is possible only in the ortho isomer because of the proximity of the donor and acceptor groups.[21] This precludes association by intermolecular hydrogen bond formation; the *meta* and *para* isomers can undergo molecular association preferentially and thus fail to supply the hydrogen bond needed to stabilize the corresponding salt with the oxine ester. Dihydroxybenzoic acids such as the 2,4 isomer (β-resorcylic acid) and the 2,5 isomer (gentisic acid) were non-reactive in ester-salt formation. These present examples of competitive hydrogen bonding—the *ortho-* hydroxyl hydrogen remains co-ordinated in a chelate ring with the *acid carbonyl* and the *meta-* or *para*-hydroxyl hydrogen associates preferentially with the *ester carbonyl*, blocking stable salt formation (Fig. 2).

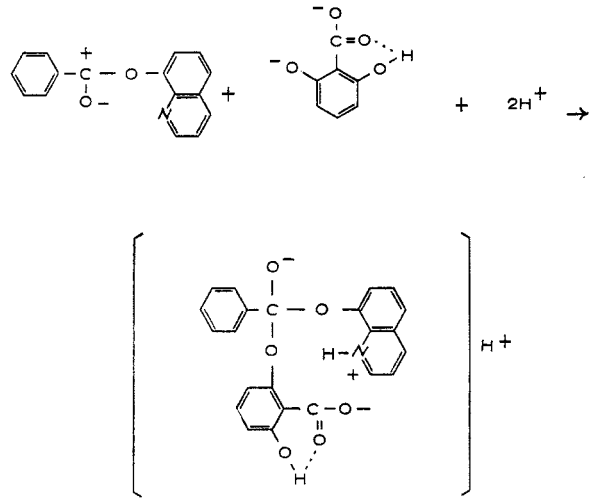

Figure 3

In our experiments 2,6-dihydroxybenzoic acid (γ-resorcyclic acid) brought about a rapid scission of the ester by hydrolysis when used as the hydrate even at low temperature in nonpolar solvents or by acid exchange under anhydrous conditions. The highly stabilized dianion of this acid can readily attack the ester carbonium ion (Fig. 3). The intermediate is decomposed in the presence of water to yield benzoic acid and the known γ-resorcylate salt of 8-hydroxyquinoline. In the absence of water rearrangement results in the formation of the salt of 8-hydroxyquinoline and γ-resorcylic acid, monobenzoate.[22]

When salicylic acids substituted with chloro, iodo, nitro, alkyl, aryl, or arylene groups were employed easily isolatable salts resulted. Ferguson

(19) R. Kuhn and O. Westphal, *Ber. deut. chem. Ges.*, **73**, 1105 (1940).

(20) M. Ito, H. Tsukioka, and S. Imanishi, *J. Am. Chem. Soc.*, **82**, 1559 (1960).

(21) A. E. Remick, *Electronic Interpretations of Organic Chemistry*, Wiley, New York (1943), p. 41.

(22) A review titled "Mechanisms of Catalysis of Nucleophilic Reactions of Carboxylic Acid Derivatives" [M. L. Bender, *Chem. Revs.*, **60**, 53 (1960)] covers analogous types of catalytic acyl-oxygen fission.

TABLE I. 8-HYDROXYQUINOLINE ESTER SALICYLATES

Salt			Formula		Analyses,[b] %		Max. Dilution Effecting
Ester	Ac	di	Mol. Wt.	M.P.[a]	Calcd.	Found	Fungistasis
8-Quinolinyl benzoate[18]	Salicylic		$C_{23}H_{17}O_5N$ 387	135.6–136.6[c]	C, 71.3 H, 4.48 N, 3.62	71.8 4.64 3.94	>1:100,000[d]
8-Quinolinyl benzoate	3,5-Diiodosalicylic		$C_{23}H_{15}O_5NI_2$ 639	175.0–175.5[e]	C, 43.2 H, 2.36 I, 39.7	43.7 2.60 39.3	<1:50,000
8-Quinolinyl benzoate	4-Methylsalicylic		$C_{24}H_{19}O_5N$ 401	135.5–136.5[e]	C, 71.8 H, 4.75 N, 3.50	71.6 4.86 3.73	1:50,000
8-Quinolinyl benzoate	3-Phenylsalicylic		$C_{29}H_{21}O_5N$ 463	149.5–150.0[c]	C, 75.3 H, 4.54 N, 3.03	76.0 4.54 3.41	>1:100,000
8-Quinolinyl benzoate	5-Chlorosalicylic		$C_{23}H_{16}O_5NCl$ 422	137–139[e]	C, 65.5 H, 3.82 N, 3.32 Cl, 8.40	65.6 3.83 3.34 8.56	1:50,000
8-Quinolinyl benzoate	3,5-Dinitrosalicylic		$C_{23}H_{15}O_9N_3$ 477	198–200[c]	C, 57.8 H, 3.15 N, 8.81	58.1 3.60 8.99	<1:50,000
8-Quinolinyl benzoate	2,3-Hydroxynapthoic		$C_{27}H_{19}O_5N$ 437	148–148.5[c]	C, 74.1 H, 4.38 N, 3.20	74.2 4.52 3.11	1:50,000
3-Methyl-8-quinolinyl benzoate	Salicylic		$C_{24}H_{19}O_5N$ 401	140–141.0[c]	C, 71.8 H, 4.75 N, 3.50	71.3 5.10 3.34	1:50,000
4-Methyl-8-quinolinyl benzoate	Salicylic		$C_{24}H_{19}O_5N$ 401	108–109.0[f]	C, 71.8 H, 4.75 N, 3.50	72.3 4.93 3.87	1:50,000
Di-8-quinolinyl phthalate	Salicylic		$C_{40}H_{28}O_{10}N_2$ 696	140–142[e]	C, 69.0 H, 4.02 N, 4.02	69.8 4.21 4.12	>1:100,000
Di-8-quinolinyl phthalate	4-Methylsalicylic		$C_{42}H_{32}O_{10}N_2$ 725	151–152[e]	C, 69.8 H, 4.45 N, 3.86	70.2 4.21 3.93	1:50,000
Di-8-quinolinyl phthalate	3,5-Diiodosalicylic		$C_{40}H_{24}O_{10}N_2I_4$ 1190	179.2–180.8[e]	C, 40.4 H, 2.02 I, 42.6	40.8 2.33 41.8	<1:50,000
8-Quinolinyl cinnamate	3,5-Diiodosalicylic		$C_{25}H_{17}O_5NI_2$ 665	144.5–146.0[e]	C, 45.1 H, 2.56 I, 38.2	45.9 3.14 37.6	>1:100,000
8-Quinolinyl butyrate[6]	Salicylic		$C_{20}H_{19}O_5N$ 353	77.0–77.5[f]	C, 68.0 H, 5.38	68.7 5.67	<1:50,000
8-Quinolinyl butyrate	3,5-Dinitrosalicylic		$C_{20}H_{17}O_9N_3$ 443	172.0–172.5[g]	C, 54.2 H, 3.84 N, 9.48	53.7 4.17 9.40	<1:50,000

Table I (*Continued*)

Salt		Formula		Analyses,[b] %		Max. Dilution Effecting
Ester	Acid	Mol. Wt.	M.P.[a]	Calcd.	Found	Fungistasis
8-Quinolinyl laurate[6]	3,5-Diiodosalicylic	$C_{28}H_{33}O_5NI_2$ 717	117.8–118.3[c]	C, 46.9	47.6	<1:50,000
				H, 4.60	4.77	
				I, 35.4	34.8	
8-Quinolinyl palmitate[6]	Salicylic	$C_{32}H_{43}O_5N$ 521	66.5–67.2[c]	C, 73.7	74.6	<1:50,000
				H, 8.25	8.48	
				N, 2.70	2.90	
8-Quinolinyl p-nitrobenzoate	Salicylic	$C_{23}H_{16}N_2O_7$ 432	160–161.5[e]	C, 63.9	64.2	<1:50,000
					3.72	3.89
				N, 6.47	6.73	
5-Chloro-7-iodo-8-quinolinyl benzoate	5-Chlorosalicylic	$C_{23}H_{14}O_5NCl_2I$ 582	160–164[e]	C, 47.6	46.8	<1:50,000
				H, 2.41	2.23	
				N, 2.41	2.32	
				Cl, 12.30	12.49	
				I, 21.80	22.38	
5-Chloro-7-iodo-8-quinolinyl benzoate	3,5-Diiodosalicylic	$C_{23}H_{13}O_5NClI_3$ 799	171–173[c,e]	C, 34.6	35.1	<1:50,000
				H, 1.63	1.25	
				Cl, 4.45	4.81	
				I, 48.5	49.2	
5,7-Dibromo-8-quinolinyl benzoate	5-Chlorosalicylic	$C_{23}H_{14}O_5NClBr$ 580	159.4–160.2[e,f]	C, 47.7	47.3	<1:50,000
				H, 2.43	1.97	
				N, 2.43	2.33	
				Br, 27.58	27.21	
				Cl, 6.05	6.35	
5,7-Dibromo-8-quinolinyl benzoate	3,5-Diiodosalicylic	$C_{23}H_{13}O_5NBr_2I_2$ 797	188–189[e]	C, 34.7	34.7	>1:100,000
				H, 1.64	1.65	
				N, 1.76	2.11	
				Br, 20.05	20.71	
				I, 31.85	32.54	
5,7-Dibromo-8-quinolinyl benzoate	3,5-Dinitrosalicylic	$C_{23}H_{13}O_9N_3Br_2$ 635	173–174[e]	C, 43.5	43.9	<1:50,000
				H, 2.06	2.19	
				N, 6.62	6.80	
				Br, 25.16	25.13	
5,7-Diiodo-8-quinolinyl benzoate	5-Chlorosalicylic	$C_{23}H_{24}O_5NClI_2$ 674	146.8–147.2[e,f]	C, 41.0	41.9	<1:50,000
				H, 2.10	2.08	
				N, 2.08	2.39	
				Cl, 5.27	5.09	
				I, 37.68	36.90	

[a] Anschutz therm (uncorr.). [b] Schwarzkopf Lab., New York, N. Y. [c] Recrystallized from 99% isopropyl alcohol. [d] Max. dilution effecting fungistasis >1:100,000 but <1:500,000 against Tricophyton gypseum and T. mentagrophytes—method of E. L. Keeney, L. Ajello, E. N. Broyles, and E. Lankford; *Bull. Johns Hopkins Hospital*, **75**, 417 (1944). [e] Benzene. [f] Petroleum ether (90–120°). [g] Dioxane.

and Kelly[23] have shown that the substitution of halogen or nitro groups in the 3-position of salicylaldehyde creates stronger hydroxy hydrogen bonding in the corresponding Schiff bases from ethylene diamine. A similar effect of hydrogen bond reinforcement can occur in the substituted salicylic acids, the ability for association by intermolecular hydrogen bonding of the acids themselves is greatly diminished, and salts are obtained.

It is interesting to note that Done[24] has compiled a comparison of some of the antirheumatic properties of salicylic acid, *m*- and *p*-hydroxybenzoic acids, and the 3-, 4-, and 5-hydroxysalicylic acids. All these compounds, with the exception of the *m*- and *p*-hydroxybenzoic acids, produced elevated plasma corticoid levels in guinea pigs. However, only salicylic acid showed activity in other related experiments. These included the stimulation of oxygen consumption in rats, the prevention of death from anaphylaxis induced in sensitized rabbits by egg albumin, and the prevention of arteritis induced in sensitized rabbits by the injection of bovine gamma globulin. Efforts to explain the selectivity observed as due to acid strength or metal chelating ability were unsatisfactory. We believe a basis for selectivity may be related to that found in our work. For example, the selective action of salicylic acid in preventing anaphylactic shock may be in its ability to occupy preferentially the reactive sites of either the antigen or antibody by the same type of co-operative bonding, ionic and hydrogen bond. It has been proved by other investigators that salicylic acid does not interfere with antigen or antibody formation but can prevent their interaction. The hydroxysalicylic acids are ineffective because the second competing hydrogen bonding group unfavorably located with respect to the carboxyl group prevents stable linkage with the antigen or antibody. Salicylic acid, as a bifunctional attacking reagent[25] towards the bifunctional reactant 8-quinolinyl benzoate, may show analogous reactivity to bifunctional reactants such as the proteins of antigens or antibodies. Although 2,6-dihydroxybenzoic acid demonstrates equally high antirheumatic properties (each hydroxyl is favorably located), it has proved extremely toxic in use. This toxicity may be a result of the catalyzed breaking of protein peptide bonds similarly to the rapid intramolecularly catalyzed fission of the oxine ester when it combined bifunctionally with the γ-resorcylic acid.

8-Quinolinyl benzoate can serve as a useful model in the study of the reactivity of bifunctional agents with proteins and enzymes of biological significance.

The first seven compounds, listed in Table I, illustrate the varied capability of 8-quinolinyl benzoate to yield salts with substituted salicylic acids. Preliminary antifungal assays indicated a high order of activity for several of these compounds and a low acute oral toxicity in rats—e.g. 8-quinolinyl benzoate, salicylic acid salt, acute oral toxicity, LD_{50} = 4.40 g. ± 0.25 g. per kg. body weight.[26]

The more active compounds listed in Table I were oxine ester salts in which there were no additional substituents in the quinoline ring, the single exception being 5,7-dibromo-8-quinolinyl benzoate, 3,5-diiodosalicylic acid salt. The most active compounds were the salicylic and 3-phenylsalicylic acid salts of 8-quinolinyl benzoate and di-8-quinolinyl phthalate, along with the 3,5-diiodosalicylic acid salt of 8-quinolinyl cinnamate.

In order to demonstrate the *in vitro* activity of the ester salt as a fungicide, 8-quinolinyl benzoate, salicylic acid salt, was formulated in an anhydrous aerosol[27] as a 0.25% by wt. solution and tested using a modification of the procedure of Oster and Golden.[28] Essentially, the method consisted in spraying lightly for five to ten seconds, 20 mm. discs cut with sterile borers from fourteen-day old plate cultures of the test organisms, then allowing *two* minutes to elapse, followed by washing the discs free of aerosol residue using suitable solvents, placing the discs face down on agar slants and incubating at 28–30° for three weeks. For control purposes the same aerosol formulation without the ester salt was used and periods as long as fifteen minutes after spraying were permitted before solvent wash. Under these conditions complete kill was observed using as test organisms fungi representing the three genera of dermatophytes *Microsporum canis* and *M. fulvum*, *Epidermophyton floccosum* and *Triciphyton gypseum*, *T. mentagrophytes*, and *T. rubrum*. All controls showed profuse growth. The details of animal and human skin sensitivity and irritation studies, as well as the results of clinical trial, will be reported elsewhere.

EXPERIMENTAL

Preparation of oxine esters. The syntheses utilized were the reaction of the 8-quinolinols with excess acid chloride as a solvent at elevated temperature or the use of near stoichometric quantities at low temperature in pyridine. Several examples of new esters are given as typical.

Di-8-quinolinyl phthalate. Thirty grams (0.21 mole) of 8-hydroxyquinoline was dissolved in 120 g. of anhydrous pyridine in a 500-ml. three neck round bottom flask equipped with a thermometer, dropping funnel, agitator, cooling bath, and a condenser vented to the atmosphere through a calcium chloride drying tube. The internal temperature was

(23) L. N. Ferguson and I. Kelly, *J. Am. Chem. Soc.*, **73**, 3707 (1951).

(24) A. K. Done, *Clin. Pharmacol. Therap.*, **1**, 141 (1960).

(25) For a discussion of bifunctional agents see M. L. Bender and Yuan-Lang Chow, *J. Am. Chem. Soc.*, **81**, 3929 (1959); G. R. Schonbaum and M. L. Bender, *J. Am. Chem. Soc.*, **82**, 1900 (1960).

(26) Food and Drug Research Lab. Inc., New York, N. Y.

(27) For composition see Experimental.

(28) K. A. Oster and M. J. Golden, *J. Am. Pharm. Assoc.*, **36**, 283, 359 (1947).

maintained at 10–15°, and over a 1.5 hr. period there was added 25 g. (0.12 mole) of phthalyl chloride. After complete addition the mixture was agitated an additional 1.5 hr. at 15–20°. It was poured into 500 ml. of water, mixed thoroughly and allowed to stand overnight. The di-8-quinolinyl phthalate was removed by suction filtration, washed well with water, and air dried at room temperature; yield 35 g. The product was crystallized from benzene (35 g. in 400 ml.) to give large, colorless prisms, m.p. 178–180°. The ester is poorly soluble in water, slightly in 99% isopropyl alcohol, readily in dilute hydrochloric acid accompanied by hydrolysis on heating.

Anal. Calcd. for $C_{26}H_{16}O_4N_2$: C, 74.2; H, 3.81; N, 6.66. Found: C, 74.8; H, 4.09; N, 6.78.

The use of the above preparative procedures yields only the diester even under conditions that favor the formation of mono-8-quinolinyl acid phthalate. In a similar experimental unit there was placed 250 g. of anhydrous pyridine. After cooling to 15°, 50 g. (0.25 mole) of phthalyl chloride was added slowly. Then, in a 0.5-hr. period a solution of 20 g. (0.14 mole) of 8-hydroxyquinoline in 50 g. of anhydrous pyridine was added. The reaction mixture was stirred an additional 2 hr. at 15°, quenched in 1 l. of water and processed as the preceding experiment. A colorless crystalline product was thus obtained; yield 28 g. (theoretical yield for the diester, 29 g) identical in m.p. and mixed m.p. with the diester.

3-Methyl-8-quinolinyl benzoate. Ten grams of 3-methyl-8-hydroquinoline and 20 g. of benzoyl chloride were mixed together and heated in an oil bath to an internal temperature of 170° for 8 hr. The molten reaction mixture was poured in a dish, allowed to solidify, and stirred, after grinding, with 100 ml. of water for 4 hr. The product was removed by suction filtration, washed with a small volume of 0.5*N* hydrochloric acid solution, and air dried; yield, 11 g. On crystallization from dimethyl ether thick, colorless prisms were obtained, m.p. 108.5–109°.

Anal. Calcd. for $C_{17}H_{13}O_2N$: C, 77.9; H, 4.94; N, 5.32. Found: C, 78.0; H, 5.27; N, 5.31.

5,7-Dibromo-8-quinolinyl benzoate. Twenty grams (0.066 mole) of 5,7-dibromo-8-hydroxyquinoline was dissolved in 250 g. of anhydrous pyridine and cooled to 10°. In a 2-hr. period 12 g. (0.085 mole) of benzoyl chloride were added, the temperature of the reaction being held at 10–15°. After complete addition the mixture was agitated for an additional 2 hr., poured into 1500 ml. of water, and allowed to crystallize. The product was suction-filtered and washed with water and 99% isopropyl alcohol; yield 18.6 g. The crude ester was recrystallized from 99% isopropyl alcohol to give colorless prisms, m.p. 147–148°.

Anal. Calcd. for $C_{16}H_9O_2NBr_2$: C, 47.2; H, 2.74; N, 3.44; Br, 39.26. Found: C, 47.3; H, 2.28; N, 3.33; Br, 39.40.

4-Methyl-8-quinolinyl benzoate melted at 123–124.2° after recrystallization from petroleum ether (90–120°).

Anal. Calcd. for $C_{17}H_{13}O_2N$: C, 77.9; H, 4.94; N, 5.32. Found: C, 78.0; H, 5.24;, N, 5.29.

8-Quinolinyl p-nitrobenzoate melted at 173–173.5° after recrystallization from benzene, (174–175° reported).

Anal. Calcd for $C_{16}H_{10}N_2O_4$: C, 65.3; H, 3.76; N, 9.53. Found: C, 65.7; H, 4.09; N, 9.43.

5,7-Diiodo-8-quinolinyl benzoate melted at 177.5–179° after recrystallization from benzene–99% isopropyl alcohol.

Anal. Calcd for $C_{16}H_9O_2NI_2$: C, 38.4; H, 1.79; N, 2.80; I, 50.6. Found: C, 39.1; H, 1.64; N, 2.90; I, 51.4.

Preparation of oxine ester salicylates. The salicylate salts were prepared by the reaction of equivalent amounts of the ester and acid in solution using 99% isopropyl alcohol, benzene, diethyl ether, dioxane, petroleum ether, or mixtures of these solvents. The products were isolated in general by crystallization at low temperature. The use of primary alcohols or esters as solvents for the reactions or recrystallizations were avoided to eliminate the possibility of alcoholysis and ester exchange. The salicylate salts are most stable in hydrocarbon and ether type solvents; in aqueous solutions hydrolysis of the ester can occur. Several typical syntheses are given.

8-Quinolyinyl benzoate, salicylic acid salt. A solution of 124 g. (0.5 mole) of 8-quinolinyl benzoate and 70 g. (0.5 mole) of salicylic acid in 1200 ml. of 99% isopropyl alcohol was prepared using heat. On slow cooling thick, colorless needles formed, yield 130 g. (see Table I for m.p. and analysis).

The ester salt was soluble, 1 g. in 3300 ml. of water at 20°, the resultant *p*H 3.9. Other solubilities obtained were:

Solvent	G./100 Ml. at 20°
Diethyl ether	3.9
99% Isopropyl alcohol	3.5
Dipropylene glycol	2.0
Dipropylene glycol monomethyl ether	9.0

The specificity of salt formation is illustrated: 6.2 g. (0.025 mole) of 8-quinolinyl benzoate and 2.9 g. (0.025 mole) of maleic acid were dissolved in 65 ml. of 99% isopropyl alcohol using heat. On cooling 5.04 g. of crystalline 8-quinolinyl benzoate was recovered. Concentration of the filtrate yielded the remainder. Repetition of attempted salt syntheses with the acids previously noted and the 8-quinolinyl benzoate in a variety of solvent systems resulted in the recovery of unchanged ester in practically quantitative amount.

8-Quinolinyl palmitate, salicylic acid salt. Three and eight-tenths grams (0.01 mole) of 8-quinolinyl palmitate and 1.4 g. (0.01 mole) of salicylic acid were dissolved in 50 ml. of 99% isopropyl alcohol with heat. On cooling no product precipitated. The volume was reduced to 25 ml. by distillation *in vacuo*, and on cooling long, colorless needles formed; yield, 3.4 g.

5-Chloro-7-iodo-8-quinolinyl benzoate, 3,5-diiodo salicylic acid salt. A solution of 5 g. (0.012 mole) of 5-chloro-7-iodo-8-quinolinyl benzoate in a mixture of 5 ml. benzene and 15 ml. of 99% isopropyl alcohol was prepared at the boiling point. There was then added 4.8 g. (0.012 mole) of 3,5-diiodosalicylic acid to give a clear solution. On cooling crystallization occurred; yield, 6.6 g.

5,7-Dibromo-8-quinolinyl benzoate, 5-chloro salicyclic acid salt. A solution of 2.9 g. (0.007 mole) of 5,7-dibromo-8-quinolinyl benzoate in 20 ml. of boiling benzene was prepared. To this hot, colorless solution there was added 1.2 g. (0.007 mole) of 5-chlorosalicyclic acid, followed by 0.5 g. decolorizing charcoal. On filtration and cooling 1.8 g. of colorless crystals were obtained as a first crop.

Low temperature hyrolysis of 8-quinolinyl benzoate with γ-resorcyclic acid hydrate. A solution of 2.5 g. (0.013 mole) of γ-resorcyclic acid $\cdot 1^1/_2$ H_2O in 150 ml. anhydrous ether was cooled to 0° and mixed with a solution of 3.2 g. (0.013 mole) 8-quinolinyl benzoate in 250 ml. of anhydrous ether, which was also precooled to 0°. Shortly on mixing a yellow precipitate formed. After standing at 0° for 20 min. the product was removed by filtration; yield; 4.5 g. of 8-hydroxyquinoline, γ-resorcylate, m.p. 150–151°. A synthetic sample of this salt prepared from 8-hydroxyquinoline and γ-resorcylic acid proved identical in melting point and mixed melting point.

8-Quinolinyl benzoate, salicyclic acid salt aerosol. The composition of the 8-quinolinyl benzoate, salicyclic acid salt, aerosol referred to in the fungicidal tests is as follows:

	Wt. %
8-Quinolinyl benzoate, salicylic acid salt	0.25
Dipropylene glycol, monomethyl ether (Dow)[a]	10.00
Trichlorofluoro methane–dichloro difluoromethane (70:30 mixture)	89.75
	100.00

[a] Prepared anhydrous, distillation.

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