Synthesis, Spectral Properties, and Antibacterial Activity of Synthetic Precursors of Macrocyclic Oxa- and Thia-Substituted Benzolactones and Benzoketones

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Abstract □ Terminally difunctional compounds were synthesized by alkylation of salicylic acid, thiosalicylic acid (*o*-mercaptobenzoic acid), or their derivatives. Whereas methyl salicylate and thiosalicylic acid were smoothly etherified, salicylic acid was alkylated at the carboxyl. Characteristic IR and NMR spectral patterns in the synthesized compounds can be attributed to intramolecular hydrogen bonding or substituent effects and are consistent with observations already reported for similar compounds. Three synthesized compounds exhibited low but reproducible inhibitory effects on *Bacillus subtilis* growth.

Keyphrases □ Salicylic and thiosalicylic acid derivatives—synthesis, spectra, and antibacterial activity as precursors of macrocyclic oxa- and thia-substituted benzolactones and benzoketones □ Antibacterial activity—synthesis and screening of salicylic and thiosalicylic acid derivatives as precursors of macrocyclic oxa- and thia-substituted benzolactones and benzoketones

Metabolites possessing a macrocyclic ring *ortho*-fused to an aromatic nucleus are few in number (1). The four known *ortho*-fused macrocyclic lactone metabolites are curvularin, monorden (radicicol), zearalenone, and lasiodiplodin. The first three, containing a keto group as well, fit the general structure of the macrolides (2); lasiodiplodin is devoid of such an additional function.

Although curvularin shows no antibacterial or antifungal activity (3), *S*-zearalenone (4) and the saturated *S*-zearalanone (5) exhibit uterotrophic activity; monorden displays strong antifungal properties with low toxicity (6). Biological testing of lasiodiplodin has apparently not yet been reported.

Previous synthetic approaches to curvularin, zearalenone, and their close structural relatives have involved closing of the aliphatic macrocyclic ring by way of an aromatic, difunctional precursor. In the case of curvularin, this procedure required a troublesome Friedel–Crafts acylation to form the aryl–carbon bond (7). The approach to preparing analogs of the naturally occurring, *ortho*-fused metabolites was to choose an aromatic starting material, with appropriate *o*-substituents already in place, and, by means of efficient standard synthetic steps, to attach one or two functionally substituted long chains at these *o*-positions.

The choice of ethers or thioethers as one of the ring-forming functional groups seemed particularly attractive. They could be derived from readily available phenols or thiophenols by the Williamson synthesis and, once formed, would be inert to a wide variety of reaction conditions. Thus, by this approach, I and II with an array of substituents X and Y would be synthetically achievable. They, in turn, would be precursors to heterocyclic analogs (IV) of the *ortho*-fused metabolites.

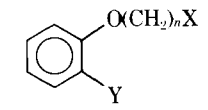
EXPERIMENTAL[1]

The following are representative preparations of compounds of types I, II, and III.

11-(2-Carboxyphenoxy)hendecan-1-ol (I: *n* = 11, X = OH, Y = COOH)—To a magnetically stirred mixture of 3.04 g (0.02 mole) of methyl salicylate, 6.0 g of anhydrous potassium carbonate, and 250 ml of dried, distilled dimethylformamide was added a solution of 5.0 g (0.02 mole) of 11-bromohendecan-1-ol (8) dissolved in 70 ml of dimethylformamide. During the addition, which required 25 min, the temperature from external heating was allowed to rise from 33 to 60°. After the mixture had been stirred and heated at 60–70° for 2.5 hr, it was filtered and the filtrate was allowed to evaporate at room temperature for 2 days and was then partitioned between 100 ml of water and 2 × 60 ml of chloroform.

The combined organic phase was washed with 2 × 50 ml of 5% NaOH, 2 × 100 ml of water, 100 ml of dilute hydrochloric acid, and 2 × 100 ml of water, dried over magnesium sulfate, and concentrated to 5.2 g of oil; this oil was distilled (112°, 0.05 torr) to remove the starting bromo alcohol. The 3.6 g of residual oil was purified by column chromatography (silica gel, chloroform eluent) to afford 3.3 g (51%) of the hydroxy ester as a light-tan oil; IR (film): 3650–3200 (OH) and 1730 ($COOCH_3$) cm^{-1}; NMR (CCl_4): δ 7.75 (m, 1, ArH), 7.18 (broad m, 3, ArH), 4.0 (t, J = 7 Hz, 1.8, $ArOCH_2$), 3.85 (s, 2.7, $COOCH_3$), 3.54 (t, J = 7 Hz, 1.8, CH_2OH), 3.0 (s, 1.0, CH_2OH), and 1.9–1.2 (m, 18.2, $—(CH_2)_9—$) ppm.

The hydroxy ester (1.5 g) was saponified with potassium hydroxide–ethanol to give 1.1 g (78%) of 11-(2-carboxyphenoxy)hendecan-1-ol, mp 81.0–81.5°; IR ($CHCl_3$): 3615 (free OH), 3530–3200 (bonded OH), and 1735 (COOH) cm^{-1}; NMR ($CDCl_3$): δ 8.32 (m, 1, ArH), 7.70 (m, 1, ArH), 7.25 (m, 2, ArH), 6.0–5.5 (broad m, 1.8, COOH and CH_2OH), 4.3 (t, J = 7 Hz, 1.9, $ArOCH_2$), 3.7 (t, J = 7 Hz, 1.9, CH_2OH), and 2.0–1.2 (m, 18.3, $—(CH_2)_9—$) ppm. The



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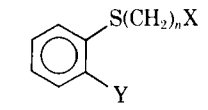

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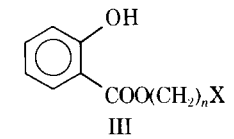

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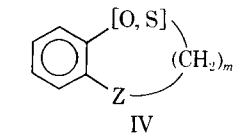


IV

X = OH, COOH, COOR
Y = COOH, COOR
Z = COO, CO, CH(OH)CO

[1] IR spectra were determined as films or solutions with a Perkin-Elmer 337 grating spectrophotometer. NMR spectra were measured in solution with a Varian A-60 or a Jeol JNM-MH-100 spectrometer. All spectra are on file in the Department of Chemistry, University of New Hampshire. Microanalyses were obtained at the University of New Hampshire with an F&M model 185 analyzer or by Galbraith Laboratories, Knoxville, Tenn. Melting points, determined with a Thomas-Hoover model 6406-H apparatus, are corrected.

Table I—Summary of Synthetic Compounds and Antibacterial Assay

Compound	Melting Point	Molecular Formula	Analysis, % Calc.	Analysis, % Found	Concentration, mg/ml Ethanol 1	Concentration, mg/ml Ethanol 0.1
					Net Zone of Inhibition, mm	
I: n = 3, X = OH, Y = COOH	107.5—109.0°	$C_{10}H_{12}O_4$	C 61.21 H 6.17	61.30 5.97	0[a]	—
I: n = 11, X = OH, Y = COOH	81.0—81.5°	$C_{18}H_{28}O_4$	C 70.10 H 9.15	70.26 9.14	0[a]	—
I: n = 10, X = $COOC_2H_5$, Y = $COOCH_3$	28.0—28.5°	$C_{21}H_{32}O_5$	C 69.20 H 8.85	69.32 8.95	0[a]	—
II: n = 11, X = OH, Y = COOH	108.5—109.0°	$C_{18}H_{28}O_3S$	C 66.63 H 8.69	66.63 8.69	9[b]	0[a]
II: n = 10, X = $COOC_2H_5$, Y = $COOC_2H_5$	29.0—29.5°	$C_{22}H_{34}O_4S$	C 66.98 H 8.67	67.14 8.72	0[a]	—
II: n = 10, X = $COOC_2H_5$, Y = COOH	72—73°	$C_{20}H_{30}O_4S$	C 65.54 H 8.25	65.65 8.36	11[b]	3[a]
III: n = 11, X = OH	41—42°	$C_{18}H_{28}O_4$	C 70.10 H 9.15	70.15 9.33	5[b]	0[a]
Salicylic acid	—	—	—	—	0[a]	—
Thiosalicylic acid	—	—	—	—	0[a]	—

[a] Average of three determinations. [b] Average of nine determinations.

broad multiplet at 6.0–5.5 ppm disappears with the addition of D_2O. The acid proton was assigned on the basis of integration. Similar behavior occurs with 11-(2-carboxythiophenoxy)hendecan-1-ol.

Ethyl 11-(2-Carboxythiophenoxy)hendecanoate (II: n = 11, X = $COOCH_2CH_3$, Y = COOH)—To a stirred mixture of 4.35 g (0.028 mole) of thiosalicylic acid and 10 g of anhydrous potassium carbonate in 300 ml of dimethylformamide was added a solution of 7.50 g (0.026 mole) of ethyl 11-bromohendecanoate (9, 10) in 100 ml of dimethylformamide over 2.8 hr; the temperature ranged from 40 to 55°. Stirring at 60° was continued for an additional 4 hr. The mixture was filtered, and the filtrate was allowed to evaporate at room temperature until a yellow solid remained. This solid was partitioned between 100 ml each of chloroform and hydrochloric acid.

The aqueous layer and residual solid material were extracted twice with 75 ml of ether. The chloroform and ether extracts were combined and concentrated. The residual solid was washed with benzene and then recrystallized from hexane to afford 3.25 g (34%), mp 72–73°; IR (CCl_4): 3300–2500 (COOH), 1734 (ester), and 1689 (acid) cm^{-1}; NMR (CCl_4): δ 12.19 (s, 1.04, COOH), 8.18 (m, 1, ArH), 7.34 (broad m, 3, ArH), 4.08 (q, 1.82, J = 6 Hz, $COOCH_2$), 2.88 (t, 1.82, J = 6 Hz, CH_2S), 2.21 (t, 1.82, J = 6 Hz, CH_2COO), and 1.90–1.00 (m, 19.6, $-(CH_2)_8-$ and CH_2CH_3) ppm.

11-Hydroxyhendecyl Salicylate (III: n = 11, X = OH)—Addition of 7.0 g (0.027 mole) of 11-bromohendecan-1-ol in 100 ml of dimethylformamide to a stirred mixture of 3.84 g (0.0278 mole) of salicylic acid, 9 g of anhydrous potassium carbonate, and 260 ml of dimethylformamide was carried out as described for II. After being stirred and heated for 7 hr, the mixture was filtered and the filtrate was evaporated to a tan solid. After being washed with water, the solid was taken up in chloroform, which was washed sequentially with 2 × 20 ml of 5% $NaHCO_3$, 2 × 20 ml of 5% NaOH, 3 × 20 ml of water, dried (magnesium sulfate), and concentrated to 3.8 g (45%) of crude oil product.

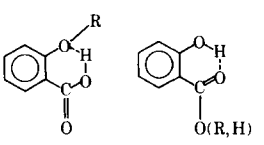
Column chromatography (silica gel, chloroform eluent) afforded 1.5 g of oil which gave, after solidification in an ice bath and three recrystallizations from hexane, 1.1 g (13%) of white crystalline solid, mp 41–42°; IR ($CHCl_3$): 3630 (free OH), 3500–3150 (bonded OH), and 1675 (ester) cm^{-1}; NMR (CCl_4): δ 10.65 (s, 0.77, ArOH), 7.80 (m, 1, ArH), 7.40 (m, 1, ArH), 6.85 (m, 2, ArH), 4.34 (t, J = 6 Hz, 1.8, $ArCOOCH_2$), 3.56 (t, J = 6 Hz, 1.8, CH_2OH), and 1.90–1.10 (m, 19.5, $-(CH_2)_9-$ and CH_2OH) ppm. Both the phenolic proton signal at 10.65 ppm and the alcohol proton signal, appearing as a singlet at 1.45 ppm, disappear with the addition of D_2O.

Antibacterial Assay—Inhibition of *Bacillus subtilis*[2] growth was measured by placing a paper disk containing 20 μl of solution on an agar surface seeded with the organism and noting zones of growth inhibition after 20 hr of incubation (11). The "net zone of inhibition" (Table I) is the total diameter of the inhibition zone (millimeters) minus the diameter of the paper disk. All compounds were also tested against the green alga *Chlorella pyrenoidosa*[3] (No. 395) (12) and found to be inactive.

RESULTS

Synthesis—Whereas the synthesis of II by alkylation of thiosalicylic acid at the sulfur proceeded smoothly, attempts at alkylating salicylic acid led, unexpectedly, to III rather than to I. In fact, this tendency of salicylic acid to undergo alkylation at the carboxyl rather than the hydroxyl was noted by Herzig in 1894 (13). Later, it was reported (14) that the benzyl ether of salicylic acid could be obtained in a Williamson synthesis, provided a large excess of alkali was employed. Apparently the dianion of salicylic acid, which would lead to alkylation at the phenolic site, is formed only with difficulty. Nozu *et al.* (15) showed that salicylic acid behaves as a typical monobasic acid on titration. Compounds of type I were obtained by alkylating salicylate esters, a reaction that proceeded as expected. Saponification of the ethereal esters led to I.

Spectral Properties—Unusual IR spectral characteristics were encountered in some of the synthetic compounds. For example, in



I (Y = COOH) III

Table II—IR Stretching Frequencies of Salicylic Acid Derivatives

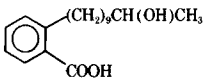
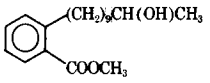
Compound	OH, cm^{-1}	C=O, cm^{-1}
o-Ethoxybenzoic acid[a]	3290	1740
11-(2-Carboxyphenoxy)-hendecan-1-ol (I: n = 11, X = OH, Y = COOH)	3615, 3530, 3200	1735
Salicylic acid, hexyl ester[b]	3175	1670
11-Hydroxyhendecyl salicylate (III: n = 11, X = OH)	3630, 3500–3150	1675

[a] "Sadtler Standard Spectra, Prism," Sadtler Research Labs., Inc. Philadelphia, Pa., 1965, No. 36382. [b] *Ibid.*, No. 3871.

[2] Difco Laboratories.

[3] Obtained from Indiana Algal Culture Collection, R. C. Starr, Bloomington, Ind.

Table III—Characteristic NMR Chemical Shifts in the Aromatic Region of *o*-Substituted Benzoic Acids and Esters

Compound	Solvent	NMR Shift δ_1[a]	NMR Shift $\delta_{2,3}$[a]	$\Delta\delta[\delta_1-(\delta_{2,3})]$
o-Methoxybenzoic acid	$CDCl_3$[b]	8.17	7.37	0.80
Methyl salicylate	CCl_4[c]	7.70	7.03	0.67
I: n = 11, X = OH, Y = COOH	$CDCl_3$	8.32	7.47	0.85
I: n = 11, X = OH, Y = $COOCH_3$	CCl_4	7.75	7.15	0.60
I: n = 10, X = $COOC_2H_5$, Y = $COOCH_3$	$CDCl_3$	8.12	7.48	0.64
III: n = 11, X = OH	CCl_4	7.80	7.12	0.68
	$CDCl_3$[d]	8.10	7.35	0.75
	$CDCl_3$[d]	7.80	7.30	0.50
I: n = 3, X = OH, Y = COOH	$(CH_3)_2SO$-d_6	7.67	7.20	0.47
I: n = 3, X = OH, Y = $COOCH_3$	$(CH_3)_2SO$-d_6	7.62	7.12	0.50
II: n = 10, X = $COOC_2H_5$, Y = COOH	CCl_4	8.18	7.34	0.84
II: n = 10, X = $COOC_2H_5$, Y = $COOC_2H_5$	CCl_4	7.95	7.25	0.70
II: n = 11, X = OH, Y = COOH	$(CH_3)_2SO$-d_6	7.98	7.42	0.56

[a] δ_1 = midpoint of low-field multiplet proton (1H), and $\delta_{2,3}$ = midpoint of up-field multiplet (3H). [b] "High Resolution NMR Spectra Catalog," vol. 1, Varian Associates, Palo Alto, Calif., 1962, No. 195. [c] "Sadtler Nuclear Magnetic Resonance Spectra," Sadtler Research Labs., Inc., Philadelphia, Pa., 1965, No. 7214M. [d] Reference 17.

I, where Y=COOH, both the OH and C=O stretching vibrations were unusually high in the regions expected for a monomeric carboxylic acid (16). This finding can be attributed to extensive intramolecular hydrogen bonding of carboxyl with *ortho*-phenolic ether oxygen. As expected, the IR spectra of the corresponding thio compounds (II) were normal, with the OH appearing as a broad band at 3300–2500 cm^{-1} and the C=O appearing at 1690 cm^{-1}. The ester carbonyl stretching band in III was, on the other hand, at an unusually low frequency, probably because of another mode of intramolecular hydrogen bonding. Precedents for these spectral features are to be found in related compounds (Table II).

The proton NMR spectra displayed distinctive features in the aromatic region. In essence, the aromatic (Ar—H) proton *ortho* to a carboxyl or ester function was shifted downfield relative to the three remaining aromatic protons. This behavior, already noted in dideoxyzearalane and two related compounds (17), seems to be generally characteristic. The extent of shift, expressed as $\Delta\delta$ (*i.e.*, separation between the lowest field Ar—H proton and the remaining three aromatic protons), is dependent on the nature of the carbonyl function, being greater for carboxylic acid than for carboxylic ester. Although the shifts are undoubtedly dependent on other factors such as solvent and additional substituents, which have not yet been clarified, the trend can be clearly seen from the examples assembled in Table III, taken from this work and published literature. This NMR pattern has been valuable in corroborating the identity of isomeric Structures I and III.

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