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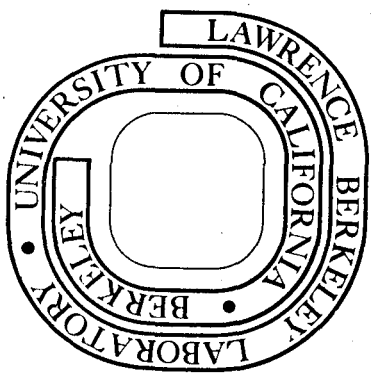

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Iron Sequestering Agents. I. Synthesis of 2,3-Dihydroxybenzamides

Summary: Both dimethyl and sulfinyl (≻SO) O-protected 2,3-dihydroxybenzoyl chloride are convenient precursors for the synthesis of 2,3-dihydroxybenzamides.

Sir:

Until quite recently, synthesis of 2,3-dihydroxybenzamides (DHB amides), one of several classes of iron sequestering agents found in nature,[1] has been limited to biosynthesis[2] or DCC-mediated condensations of amino acids with DHB acid.[3] Recently, the tetra-DHB amides of tetraazacyclams have been prepared via amidation of 2,3-dioxomethylenebenzoyl chloride followed by BCl_3 removal of the methylene O-protecting group.[4] A carbocyclic analog[5] of enterobactin was synthesized making use of the acid-labile acetonide protecting group.

This work describes the use of the readily available 2,3-dimethoxybenzoyl (DMB) chloride in the synthesis of new DHB amides (Tables I and II) prepared as model iron sequestering agents. Also the synthetic facility of the previously unreported 2,3-dioxosulfinylbenzoyl chloride 1 has been demonstrated in the synthesis of DHB amide, 4. Subsequent to amidation of the acid chloride, the O-methyl and sulfite protecting groups were removed with BBr_3 and H_2O, respectively.

The experimental procedures employed are typified by the following descriptions of the synthesis of 2,3-dihydroxy-N,N-dimethylbenzamide 4:

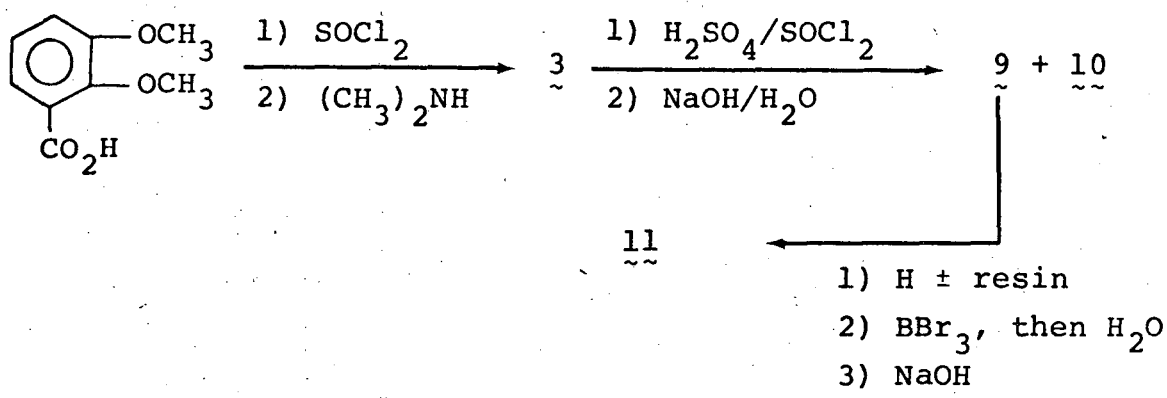
(Method A.) Treatment of DMB chloride (6.0 g, 30 mmol) with excess dimethylamine in benzene solution followed by a water wash, gave after (*in vacuo*) evaporation of the benzene, the corresponding amide 3, 5.9 g (92%). Then 3, 5.8 g (28 mmol) in 25 ml CH_2Cl_2, under argon, was added dropwise (15 min) to a vigorously stirred BBr_3 (5 ml, 53 mmol) in 25 ml CH_2Cl_2 solution (cooled by an ice bath). The resulting slurry was stirred several hours at ambient temperature, then 20 ml H_2O added dropwise to hydrolyze the boron compounds. Next co-evaporation with MeOH to remove methylborates followed by fractional sublimation at 115° (< 1 mm Hg) gave pure 4 (55%).
(Method B.) A benzene solution of 2,3-dioxosulfinylbenzoyl chloride, 12, [mp 84-6°; mass spectrum m/e (rel intensity) 218 (M, 51), 183 (M-Cl, 77), 135 (M-Cl-SO, 71), 107 (M-Cl-SO-CO, 85)] was treated with excess dimethylamine. The reaction mixture was filtered to remove $NEt_3 \cdot HCl$ then evaporated to a residue. Trituration with H_2O for several hours gave a pungent SO_2 odor. Filtration gave 1.8 g and a $CHCl_3$ extract of the H_2O layer gave additional 0.6 g solid. Combined solids were sublimed as above to obtain 4, 2.3 g (79%): mp 182-5°. A mixed melting point of this material with that produced by Method A was identical.

Enterobactin was reportedly[6] synthesized by direct amidation of the appropriate triamine with DHB chloride, the latter prepared by refluxing an $SOCl_2$ solution of DHB acid for 5 hrs. Evaporation of the $SOCl_2$ followed by sublimation

gave a product with mp 84-6°. We have prepared 12 in precisely the same way and identified it as the O-sulfinyl protected analogue of DHB chloride. The preparation of catechol sulfite by reaction of catechol with $SOCl_2$ has been described.[7]

Procedures for the synthesis of the 4-X-DHB amides (8, X = 4-NO_2; 11, X = 4-SO_3Na) were based upon DMB acid rather than DHB acid to avoid possible oxidation and esterification side reactions. Both nitration of DMBA ($AcOH/HNO_3$) and sulfonation of 4 ($H_2SO_4/SOCl_2$) gave solely monosubstituted isomeric mixtures consisting of 61/39 (5/6) and 70/30 (9/10). This was determined by elemental analyses (Table II) and ^{1}H-NMR spectra[8] of the crude isomeric mixtures. In both cases, the pure isomers were obtained by recrystallization from the appropriate solvent(s) (Table I).

In every case, acid chlorides were prepared in a reaction with $SOCl_2$ except for 5 which required PCl_5 for better yields in the subsequent amidation step to produce 7. The 4-X-isomers, 7 and 9, were chosen for deprotection as the major isomer which would be easiest to produce in larger amounts. The O-demethylation of 9 necessitated prior treatment with cation exchange resin to produce the CH_2Cl_2-soluble sulfonic acid which was treated in the usual manner with excess BBr_3/CH_2Cl_2. After hydrolysis of the boron compounds and volatilization as the methyl borates, 11 was isolated at pH 3-4 as the monosodium salt.



In this work we have chosen to prepare dimethylbenzamides for reasons of design, good water solubility, and ease of evaluation. Compounds 4, 8, 11 are new, potentially useful iron sequestering agents. Their evaluation as such will be reported elsewhere.

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8. The δ 7-8 region of the ^{1}H-NMR of both crude isomeric mixtures consisted of two AB quartets: 5 (DMSO), 7.87 and 7.97 (J_{AB} = 3 Hz); 6 (DMSO), 7.27 and 8.03 (J_{AB} = 9 Hz); 9 (D_2O), 7.35 and 7.60 (J_{AB} = 2 Hz); 10 (D_2O), 7.35 and 7.82 (J_{AB} = 9 Hz).
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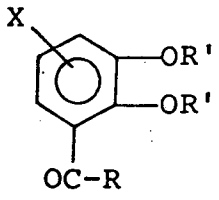
Table I. 2,3-Dihydroxybenzamides and Precursors



No.	X	R	R'	mp, °C (recrystn solvent)	% Yield[a]
1	H	$-NH_2$	CH_3	90-2 (H_2O)[b]	71
2	H	$-NH_2$	H	167-8.5 (H_2O)[c]	71
3	H	$-N(CH_3)_2$	CH_3	oil	92
4	H	$-N(CH_3)_2$	H	183-5 (sublimed)	55
5	4-NO_2	-OH	CH_3	173-5 (MeOH)	42
6	6-NO_2	-OH	CH_3	182-5[d,e]	35
7	4-NO_2	$-N(CH_3)_2$	CH_3	79-81[f]	92
8	4-NO_2	$-N(CH_3)_2$	H	237.5-9.5 (EtOH)	77
9	4-SO_3Na	$-N(CH_3)_2$	CH_3	233-6 (EtOH/EtOAc)[g]	46
10	6-SO_3Na	$-N(CH_3)_2$	CH_3	310-3 (EtOH)	17
11	4-SO_3Na	$-N(CH_3)_2$	H	308-9 dec	68
12	H	-Cl	-SO-	84-6[h] (sublimed)	93

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[a]Yields from Method A procedures. [b]Lit.[9] mp 93-4°. [c]For the biosynthesis of 2; see ref. 10. [d]Lit.[11] mp 185°. [e]Pure 5 was obtained from mixtures of 5 + 6 by recryst. from MeOH. The remainder was triturated with hot $CHCl_3$ to leave behind 6. [f]Crystallized from the neat liquid state. [g]Pure 10 was obtained from mixtures of 9 + 10 by recryst. from EtOH. The hot EtOH mother liquor was adjusted to turbidity with EtOAc to obtain 9. [h]Refluxing solutions of DHB acid in $SOCl_2$ react to consume two moles of $SOCl_2$ to produce 12.

Table II. Elemental Analyses

Compd.	Calcd., %						Found, %					
	C	H	N	S	Cl	Na	C	H	N	S	Cl	Na
2	54.90	4.61	9.15				54.95	4.59	9.03			
3	63.14	7.23	6.69				62.99	7.14	6.47			
4	59.66	6.12	7.73				59.29	6.06	7.60			
5 + 6[a]	47.58	3.99	6.17				47.57	4.04	6.15			
7	51.97	5.55	11.02				51.78	5.49	10.86			
8	47.79	4.46	12.38				47.95	4.58	12.14			
9, 10[a,b]	40.12	4.89	4.25	9.74			39.99	4.57	4.14	9.76		
11				11.32		8.12				11.46		9.02
12				14.64	16.25					14.64	16.33	

[a]Isomeric mixtures analyzed to prove monosubstitution.

[b]Analyzed as 9 + 10·H_2O.

Abstract: A general synthesis for (4-X)-2,3-dihydroxybenzamides (2, X = H; 4, X = H; 8, X = NO_2; 11, X = SO_3Na) is described. Both dimethyl and the previously unreported sulfinyl (>SO) O-protected (12) 2,3-dihydroxybenzoyl (DHB) chloride are convenient precursors for the synthesis of DHB amides (e.g. 4). To avoid possible side reactions, 2,3-dimethoxy (rather than 2,3-dihydroxy) benzoic acid was used in the synthesis of the NO_2 (5, X = 4-NO_2; 6, X = 6-NO_2) and the SO_3Na (9, X = 4-SO_3Na; 10, X = 6-SO_3Na) precursors. Subsequent to amidation, the methyl and sulfinyl protecting groups were removed with BBr_3 and H_2O, respectively.

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