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Approaches to and Synthesis of Chalcone Amides

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by

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A series of "chalcone" amides have been prepared. These amides are unique in the position of the substituted hydroxy and methoxy functional groups. Early approaches to the synthesis of the amides proved difficult when preparing intermediates from the phenolic substituents. These phenols were then protected to lead to easier formation of the intermediates, and then deprotected to yield the corresponding chalcone amides. The approaches to the preparation of these compounds is presented, along with the physical data used to characterize the chalcone amides.

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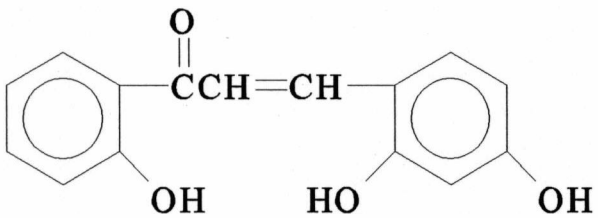
INTRODUCTION AND HISTORICAL

For several years now, AIDS (Acquired Immune Deficiency Syndrome) has generated much controversy due to its fatal nature and lack of a good treatment. Known to be a RNA containing retro virus, the AIDS virus undergoes replication on a RNA template with the assistance of a reverse transcriptase enzyme. This process reverses the usual information flow (DNA to RNA) in a cell, thereby producing DNA on an RNA template (Foye, 1989). The challenge to producing an anti-AIDS drug lies in the inhibition of the virus replication process, without affecting normal cellular metabolic processes. Since reverse transcriptase (RT) is essential for virus replication, and more importantly, has no closely related identified cellular homologs, RT is the target for antiviral therapy against AIDS. 3'-azido-2',3'-dideoxythymidine (AZT), is an example of a nucleoside analog inhibitor of Human Immunodeficiency Virus Reverse Transcriptase (HIV-RT), however, toxicities associated with AZT and resistance to this drug limit its effectiveness.

Recently, several new nonnucleoside inhibitors have been prepared which block human immunodeficiency virus type 1 (HIV-1) replication. Bis(heteroaryl)piperazines (BHAP) have been prepared which inhibit HIV-1 RT at concentrations 2 to 4 orders of magnitude lower than that which inhibits normal cellular DNA polymerase activity (Romero, 1991). Tetrahydo-imadazo[4,5,1-jk][1,4]-benzodiazepin-2(1H)-one and -thione (TIBO) derivatives have been prepared which

were shown to inhibit HIV-1 at concentrations 10^5 to 10^6 times lower than the cytotoxic concentration (Pauwels, 1990). These nonnucleoside compounds may be acting as allosteric inhibitors and may be binding on an allosteric site on the binary or on a ternary complex of the enzyme. At Western Michigan University, a sample submitted to the National Cancer Institute for *In Vitro* Anti-HIV drug screening by Dr. R. E. Harmon has shown activity against HIV-1. This compound, believed to be 2',2,4-trihydroxychalcone **(1)**, was almost as active as AZT in the preliminary screening.



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In addition to non-nucleoside inhibitors of HIV type viruses, Ishitsuka reports the effects of some chalcones on the Human Rhino Virus, another type of RNA virus. Specifically, several "chalcone" amides were prepared which exhibited 4.5 to 10 times the activity of the chalcones (Ishitsuka, 1990). These amides, 4-ethoxy-2-hydroxy-6-methoxy-N(4-methoxybenzyl)benzamide and 4-butenoxy-2-hydroxy-6-methoxy-N(4-methoxybenzyl)benzamide, were found to competitively inhibit the binding of 2',4-dihydroxy-4'-ethoxy-6'-methoxychalcone. Such differences were believed to be due to

the alteration in the binding affinities of compounds due to the variations in the shape and size of the hydrophobic pocket. Based on these results, and the activity shown by 2',2,4-trihydroxychalcone against HIV, several "chalcone" amides analogs were prepared.

STATEMENT OF PROBLEM

The purpose of this work is to prepare chalcone analogs of the 2',2,4-trihydroxychalcone, replacing the methine carbon of the chalcone with a nitrogen. In addition, several other "chalcone" amides were to be prepared, varying the placement and type of substituent. The general structure for these amides is given in Figure 1.

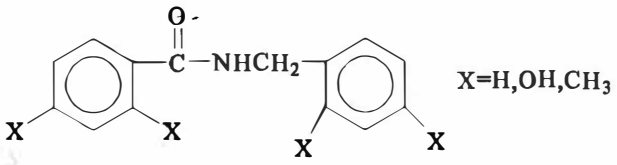


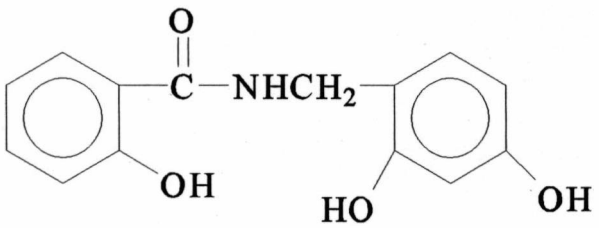
Figure 1. General Structure for "Chalcone" Amides.

Once synthesized, this compound could be sent out for *In Vitro* Anti-HIV drug screening, in the hopes that the same increase observed by Ishituka in the HRV study would apply to the HIV tests.

RESULTS AND DISCUSSION

Formation of 2-Hydroxy-N(2,4-dihydroxybenzyl)benzamide

For the synthesis of 2-hydroxy-N(2,4-dihydroxybenyl)benzamide (**2**), 2,4-dihydroxybenzylamine, which is not commercially available, was to be prepared and then coupled to salicylic acid using dicyclocarbodiimide (DCC) to give the amide.



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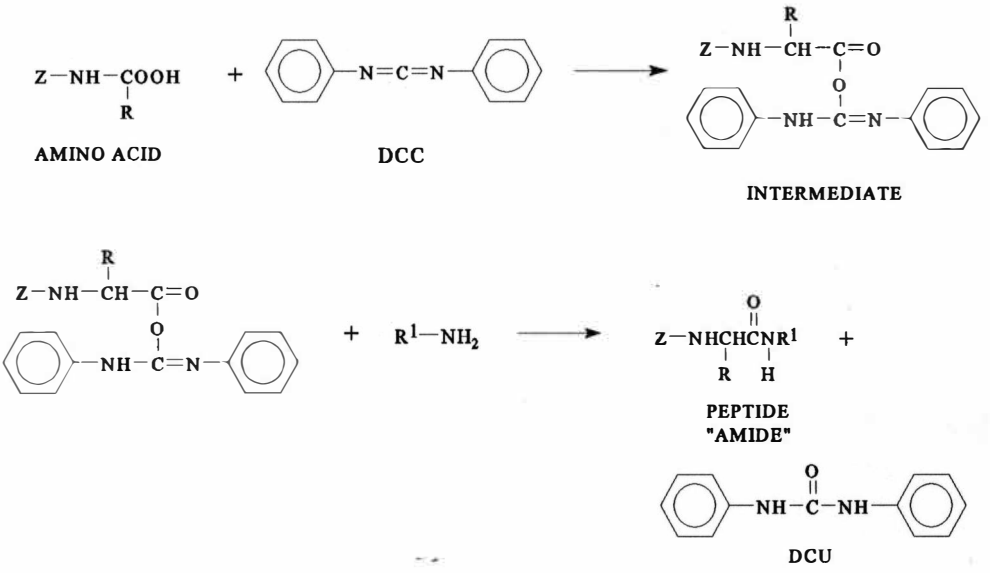
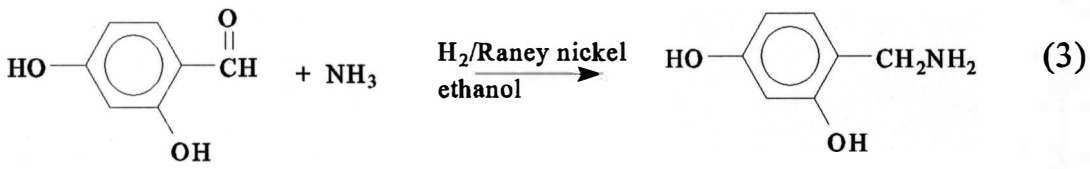
This procedure is frequently used in the synthesis of peptides (Klausner and Bodansky, 1972), the reaction scheme for this amide being given in equations 1-2.

The first step involves addition of the salicylic acid to DCC to form an intermediate. Attack on the DCC portion of the intermediate by 2,4-dihydroxybenzylamine yields a good leaving group, which upon further displacement by the amine gives the desired amide and dicyclohexylurea (DCU). The DCU is insoluble in most solvents and can be readily separated from the reaction medium by filtration.

The general reaction scheme for the formation of the amine using reductive



amination is given in equation 3, (Winans, 1966).



In solution, nucleophilic attack by ammonia on the aldehyde gives an imine, which upon reduction by hydrogen in the presence of a catalytic amount of Raney nickel yields the amine. The initial attempt at synthesizing 2,4-dihydroxybenzaldehyde gave a highly colored oily red solid. At this point, it was postulated that Schiff base (3), had been formed due to the excess amount of water used in the reaction, equations 4-5. As can be seen in equation 4, excess water drives the reaction towards the starting material. Once some amine has been formed, it reacts with the aldehyde, resulting in

$$Ar{-}CHO + NH_3 \longrightarrow ArCH{=}NH + H_2O \quad (4)$$

excess water

$$ArCH{=}NH + Ar{-}CHO \rightleftharpoons ArCH_2N{=}CHAr + NH_3 \quad (5)$$

3

amination to the Schiff base. These complexes are often strongly colored, due to the increase in conjugation within the molecule, and in this case, the presence of phenol groups. A repeat of this experiment using anhydrous conditions and excess ammonia to drive the equilibrium to the imine gave several colored solids. Recrystallization of these solids and FTIR analysis did not show the expected primary N-H stretches around 3400 cm^{-1} and 3350 cm^{-1}. GC-MS analysis gave several peaks on the chromatograph indicating the solids as still being mixtures. Examination of the fragmentation for each peak on the mass spectrograph suggested that stable hydrobenzamides and possibly their intermediates were being formed, Figure 2. The presence of *ortho* and *para* hydroxy substituents may be hydrogen bonding with the intermediate hydroxyamines, leading to increased stability and further reaction with the aldehyde. It is also possible that resonance effects may be present due to these *ortho* and *para* substituted hydroxyl groups. This through resonance may be reducing the susceptibility of the aldehyde carbon to nucleophilic attack by the ammonia.

A synthesis of 2,4-dihydroxybenzylamine from 2,4-dihydroxybenzaldehyde was tried using sodium cyanoborohydride and ammonia acetate, equations 6-7.

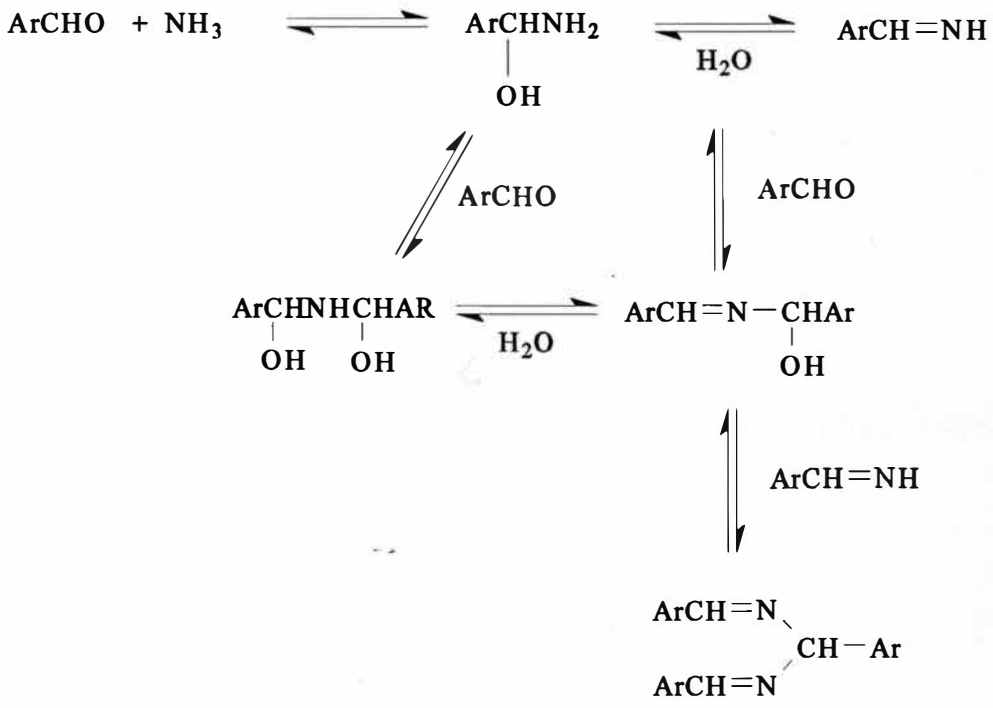
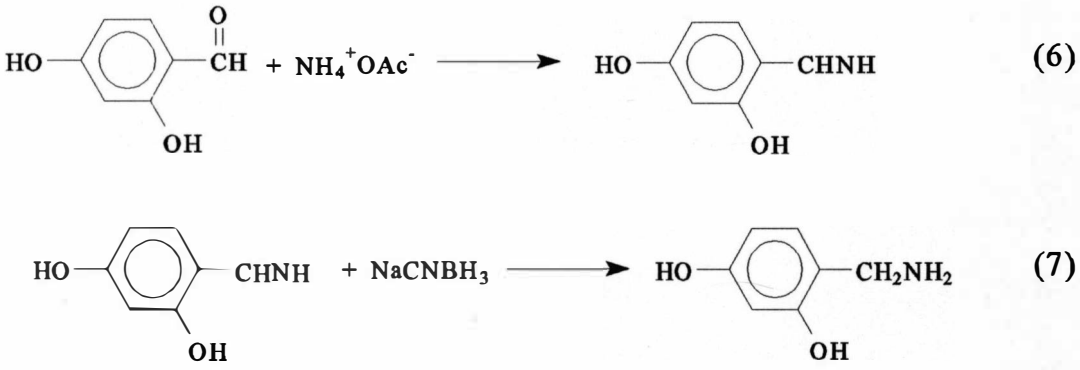


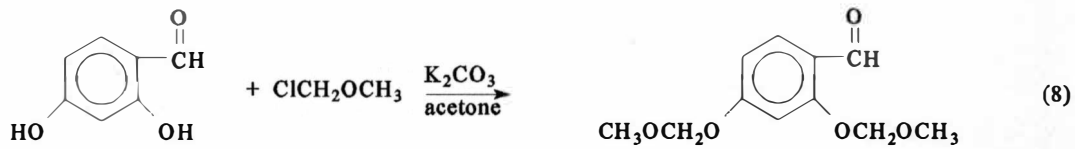
Figure 2. Intermediates in the Formation of Hydrobenzamides, (Ogata, 1964).



Here, ammonium acetate attacks the aldehyde to give the imine, which is then reduced in the same solution by sodium cyanoborohydride. Workup of the solution gave a thick, black, tar-like material which could not be recrystallized or distilled into a

purified product.

The presence of the hydroxyl groups seemed to be interfering with the synthesis of the amine. Therefore, attempts were made to protect the phenols with ethers before forming the amine. An arylmethoxymethyl ether was considered first due to it's stability to basic conditions, and easy cleavage in acidic medium. Once the phenols had been protected and the amine was formed, amide formation via a modified Schotten-Baumann method with an acid chloride could be used, provided other substrates were protected as needed. These amides could then be cleaved easily under acidic conditions to give the desired amide. Given below are the three reactions used in the attempted synthesis of 2,4-dimethoxymethoxybenzaldehyde, equations 8-10. Reaction proceeds by way of initial formation of the phenoxide sodium salt, and then reaction with the chlorodimethyl ether to give the protected aldehyde. In each



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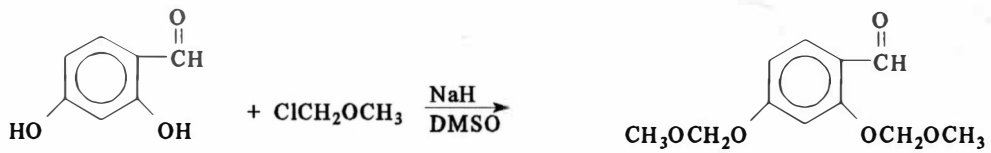

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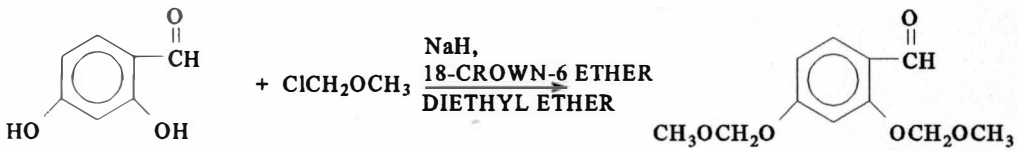
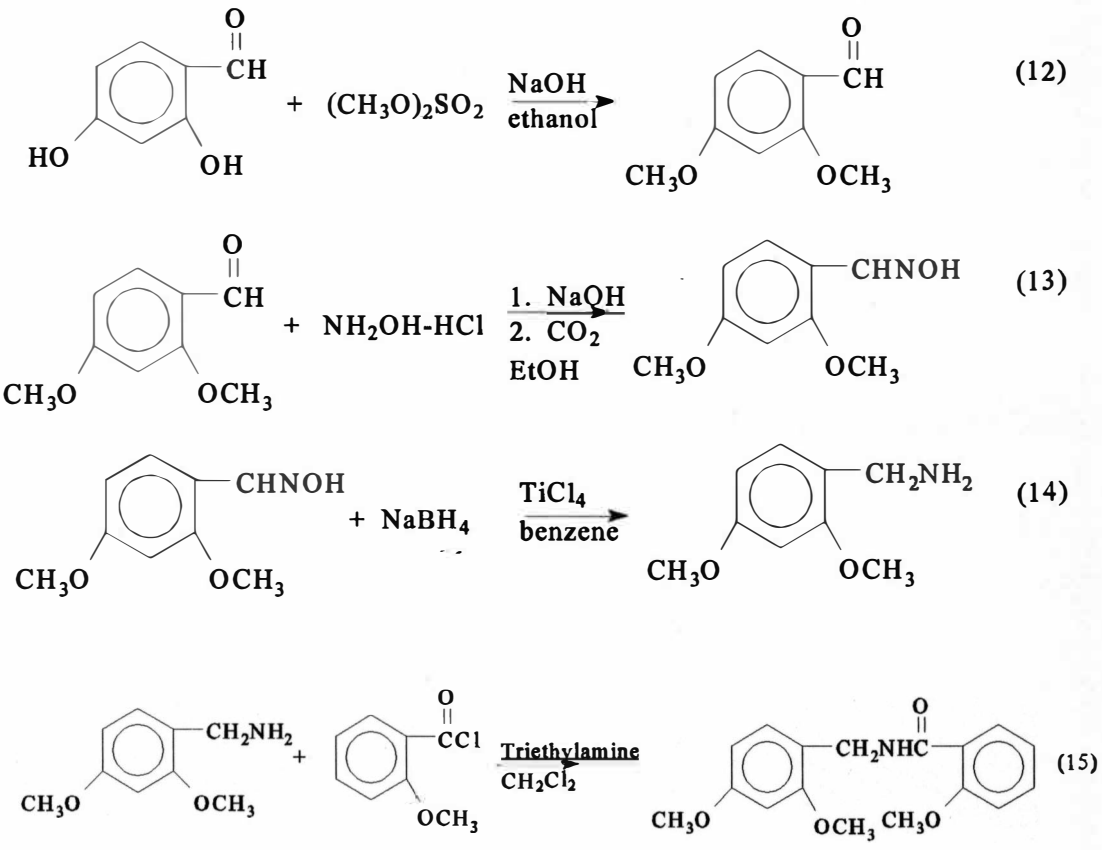


(10)

synthesis, only a small amount of protected aldehyde (less than 10% yield) was believed to have been made. In the case of the reactions given by equations 8 and 10, the difficulty of forming the initial salt due to the poor solubility of the base in the reaction solvent was thought to be the primary hindrance in forming the protected aldehyde. For the reaction run in DMSO, the sodium salt was soluble, but a separation of the suspected protected aldehyde from DMSO proved difficult, resulting in reduced yields.

Due to the difficulty of making the aryl methoxymethyl ethers, the phenols were protected with methyl ethers in high yields. From 2,4-dimethoxybenzaldehyde, 2,4-dimethoxybenzaldehyde oxime was made, which upon reduction by $NaBH_4$ in the presence of a catalytic amount of $TiCl_4$ gave 2,4-dimethoxybenzylamine. The reactions for these syntheses are given in equations 12-14. The experimental results for these compounds are found in the experimental section.

Once the amine had been prepared, formation of a protected amide was tried using a modified Schotten-Baumann method, wherein the 2,4-dimethoxybenzylamine reacts with *o*-anisoyl chloride in the presence of base to give 2-methoxy-N(2,4-dimethoxybenzyl)benzamide, equation 15. By using triethylamine to scavenge the HCl formed in the reaction, one equivalent of amine per one equivlent of acid chloride was used, thereby reducing the amount of amine needed to make the desired amide. The triethylamine salt is then easily removed by washing with water. Examination of the



data in Tables 1,2,3 shows structural data consistent with that of 2-methoxy-N(2,4-dimethoxybenzyl)benzamide for the resulting heavy, viscous liquid.

Table 1

FTNMR of 2-Methoxy-N(2,4-dimethoxybenzyl)benzamide
(DMSO-d_6)

δ(ppm)	no. of hydrogens	peak type	assignment	J(Hz)
3.77,3.86,3.88	9	singlets	methoxys	
4.58	2	doublet	methylene	0.03
6.48-7.92	7	multiplets	aromatics	
8.55	1	broad	amide	

Table 2

FTIR of 2-Methoxy-N(2,4-dimethoxybenzyl)benzamide
(NaCl plate)

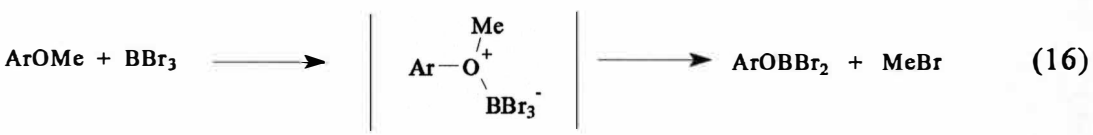
wavelength cm^{-1}	intensity	assignment
3405	strong	amide N-H stretch
2950	moderate	methyl C-H stretch
1651	strong	amide C=O stretch

Table 3

GC-MS of 2-Methoxy-N(2,4-dimethoxybenzyl)benzamide
(Methanol)

m/z+	fragmentation	
301	$(CH_3O)_2C_6H_3CH_2NHCOC_6H_4(OCH_3)$	molecular ion peak
167	$(CH_3O)_2C_6H_3CH_2NH$	
135	$(CH_3O)C_6H_4CO$	

2-Hydroxy-N(2,4-dihydroxybenzyl)benzamide was to have been prepared by demethylation of the above liquid using BBr_3. The reaction proceeds via a complex formed between the reagent and the ethereal oxygen atoms, equations 16-17, (McComie, 1978). This complex is then destroyed by hydrolysis in water or methanol.



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(17)

Using the boron tribromide method, a white solid was obtained in 98% yield. The data in Tables 4,5,6 appear to give results expected from that of 2-hydroxy-N(2,4-dihydroxybenzyl)benzamide. Phenols were assigned based on NMR assignments found with similar compounds (Sadtler, 1971). The presence of the free phenols and fragmentation pattern found by GC-MS seemed to indicate that the expected amide had been formed. However, combustion analysis gave 8.5% residue, suggesting that the boron tribromide had actually formed a complex with the amide which was not hydrolyzed with the addition of water. Such complexes are known to occur (Gerrard,

Table 4

FTNMR of BBr_3 Cleavage Product of 2-Methoxy-N(2,4-dimethoxybenzyl)benzamide (DMSO-d_6)

δ(ppm)	no. of hydrogens	peak type	assignment	J(Hz)
4.35	2	doublet	methylene	0.03
6.06-8.29	7	multiplet	aromatic	
7.10	1	broad	amide	
9.22	1	broad	phenol	
9.74	1	broad	phenol	

Table 5

FTIR of BBr_3 Cleavage Product of 2-Methoxy-N(2,4-dimethoxybenzyl)benzamide (KBr pellet)

wavelength cm^{-1}	intensity	assignment
3200-3600	broad, strong	O-H stretch
1646	strong	amide C=O stretch

Table 6

GC-MS of BBr_3 Cleavage Product of 2-Methoxy-N(2,4-dimethoxybenzyl)benzamide (Methanol)

m/z+	fragmentation
137	$(HO)_2C_6H_3CH_2NH$
121	$(HO)C_6H_4CO$

1961), but simple hydrolysis with water or methanol is usually sufficient enough to destroy the boron tribromide complex. The presence of the three phenol peaks suggests that the boron tribromide is not forming a stable borate ester between the phenol groups. Instead, these boron trihalides are believed to coordinate at the carbonyl oxygen of the amide. This particular complex is probably stabilized by resonance with the lone pairs of the nitrogen or by the through resonance of the aromatic ring due to the presence of the electron donating hydroxy groups. Such a complex should result in a decrease in the C=O stretching, which in fact is seen from a value of 1657 cm^{-1} for the protected amide to 1642 cm^{-1} for the deprotected amide. However, hydrogen bonding between the phenol groups and carbonyl oxygen might also explain this decrease.

Attempts to destroy the suspected boron tribromide complex were unsuccessful. Hydrolysis using sodium hydroxide in methanol at room temperature was too slow, and attempts to decrease the time for hydrolysis by heating did not give any of the desired amide.

Due to the difficulties in trying to remove the aryl methoxy group, protection of the phenol groups on the aldehyde using chloromethylethyl ether was tried. In this case, Adogen 464, a phase transfer catalyst, was used in order to help increase the solubility of the phenoxide salt in the organic layer. Figure 3 gives the general scheme for formation of 2,4-diethoxymethoxybenzaldehyde.

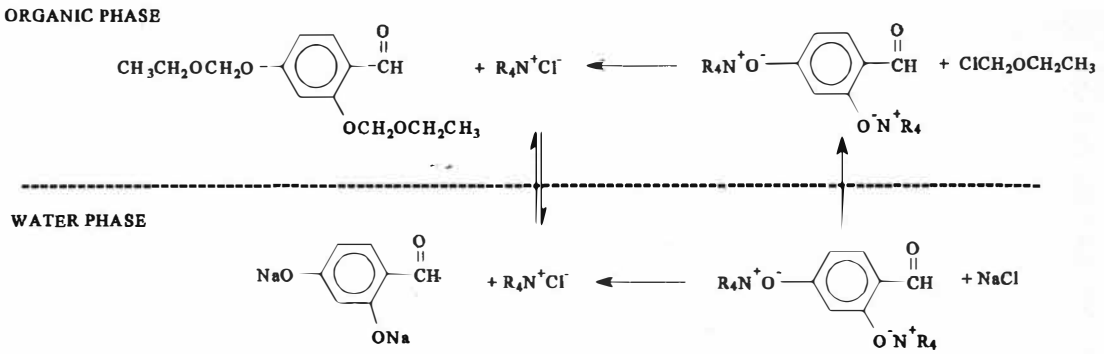


Figure 3. Schematic for Formation of 2,4-Diethoxymethoxybenzaldehyde Using Adogen 464 as a Phase Transfer Catalyst.

FTNMR gave peaks at 1.22, 3.74, and 5.26-5.32 ppm, confirming the presence of the methylethyl ether group. Also, FTIR analysis did not show the broad O-H stretch in the region 3200-3600 cm^{-1}, which would be expected due to any unprotected product.

In addition to the procedure using Adogen 464 as a phase transfer catalyst, this reaction was run in N,N'-dimethylformamide (DMF) with NaH and the chloromethylethyl ether. Due to the low boiling point of DMF under reduced pressure, separation of the resulting product by distillation was possible.

The protected aldehyde was then reductively aminated using the method given

for the unsuccessful reductive amination of 2,4-dihydroxybenzaldehyde. The absence of an aldehyde C=O stretch at 1682 cm^{-1} and the presence of two peaks at 3400 cm^{-1} and 3310 cm^{-1} due to N-H stretching is strong evidence of the formation of the amine. Because these compounds were used in the synthesis of 2-hydroxy-N(2,4-dihyroxybenzyl)benzamide which was proven to be chemically pure, we can infer that 2,4-diethoxymethoxybenzaldehyde and 2,4-diethoxymethoxybenzylamine were successfully prepared.

A protected amide intermediate was then formed using 2,4-diethoxymethoxybenzylamine and commercially available *o*-acetylsalicyloyl chloride using the modified Schotten-Baumann method. A pink oily liquid was the result of this synthesis and GC-MS results suggested that a mixture of protected and partially protected compound existed, probably due to the hydrolysis of the aryl ethers occurring during the acid washing to remove the excess triethylamine. Instead of isolating this intermediate, the liquid was dissolved in methanol and the protection groups removed by hydrolysis with acid. Workup of the solution, gave a yellow solid that decomposed above 50^0C. Spectral data for this compound is given in Tables 7,8,9. The GC-MS shows fragmentation consistent with the deprotected amide although a molecular ion peak is not present, probably due to the low decomposition temperature of the amide. In addition, FTIR shows the expected broad O-H stretch with absence of any C=O stretches due to acetyl protecting groups. Combustion analysis found %C=65.1%, H=5.11%, N=5.6%, O=24.2% which was within

experimental error of the theoretical values of %C=64.9%, H=5.06%, N=5.41%,

Table 7

FTNMR of 2-Hydroxy-N(2,4-dihydroxybenzyl)benzamide
(DMSO-d_6)

δ(ppm)	no. of hydrogens	peak type	assignment	J(Hz)
4.35	2	doublet	methylene	0.03
6.06-6.80, 7.09-8.29	7	multiplet	aromatic	
7.10	1	singlet	amide	
9.22	1	broad	phenol	
9.74	1	broad	phenol	
11.49	1	broad	phenol	

Table 8

FTIR of 2-Hydroxy-N(2,4-dihydroxybenzyl)benzamide
(KBr pellet)

wavelength cm^{-1}	intensity	assignment
3200-3600	broad, strong	O-H stretch
1646	strong	C=O stretch

Table 9

GC-MS of 2-Hydroxy-N(2,4-dihydroxybenzyl)benzamide
(Methanol)

m/z+	fragmentation
137	$(HO)_2C_6H_3CO$
121	$(HO)C_6H_4CH_2N$

O=24.7%. These results, including the absence of protection groups as indicated by FTNMR analysis are evidence for the purity and presence of 2-hydroxy-N(2,4-dihydroxybenzyl)benzamide.

Formation of 2,4-Dihydroxy-N(2-hydroxybenzyl)benzamide

Based on the synthesis of the previous amide, 2,4-dihydroxy-N(2-hydroxybenzyl)benzamide was to have been prepared using protection of the phenols, formation of the intermediate amide, and then deprotection to the desired product. At the time, combustion analysis had not been performed on the amide formed via boron tribromide cleavage, and cleavage of the aryl methyl ethers was thought to be the best route based on the spectral data given. The attempts to form the desired amide from 2,4-dimethoxy-N(2-hydroxybenzyl)benzamide were unsuccessful, but did lead to some interesting speculation on the use of boron tribromide as a cleavage agent. The spectral data for this compound is given in Tables 10,11,12. Examination of FTNMR analysis gives a peak corresponding to a methoxy group, however integration of the signal does not give 3 hydrogens for this compound. This suggested that the amide was only being partially cleaved and a mixture of deprotected and protected amide existed.GC-MS data for this amide shows 4 peaks at 278, 280, 282, and 284 m/z+ in the approximate ratio of 1:3:3:1. This is characteristic of a tribromide and strongly suggests that the boron tribromide is coordinating to the amide according to the fragmentation pattern given in table 10. In addition, FTIR gives a strong, broad signal

at 1617 cm^{-1}, much lower than that expected for a C=O stretching frequency. This

Table 10

FTNMR of BBr_3 Cleavage Product of 2,4-Dimethoxy-N(2-methoxybenzyl)benzamide ($DMSO-d_6$)

δ(ppm)	no. of hydrogens	peak type	assignment	J(Hz)
3.85	2	singlet	methoxy	
4.6-5.0	1	broad	amide	
6.4-8.17	7	multiplet	aromatic	
9.79	1	singlet	phenol	
11.69	1	broad	phenol	

Table 11

FTIR of BBr_3 Cleavage Product of 2,4-Dimethoxy-N(2-methoxybenzyl)benzamide (KBr Pellet)

wavelength cm^{-1}	intensity	assignment
3150-3500	broad	O-H stretch
1617	strong	C=O stretch

Table 12

GC-MS of BBr_3 Cleavage Product of 2,4-Dimethoxy-N(2-methoxybenzyl)benzamide (Methanol)

(m,m+2,m+4,m+6)/z+	fragmentation
355	$(C_6H_4)CH_2NHBBr_3$
278,280,282,284	CH_2NBBr_3
264,266,268,269	$NBBr_3$
208	$(C_6H_3)CONHCH_2(C_6H_4)$

may be indicative of the coordination of the boron tribromide complex at the carbonyl oxygen as had been suggested previously. The presence of two hydroxyl groups on the benzamide portion of the amide may be providing enough through resonance to lead to an even more stable complex than seen with the previous amide. This insoluble complex may then be precipitating prematurely resulting in some still unprotected phenols. After reacting with sodium hydroxide in methanol, GC-MS showed the presence of two compounds with a m/z+ of 259 and 273, results consistent with those expected for a fully deprotected and partially deprotected amide, Figure 4.

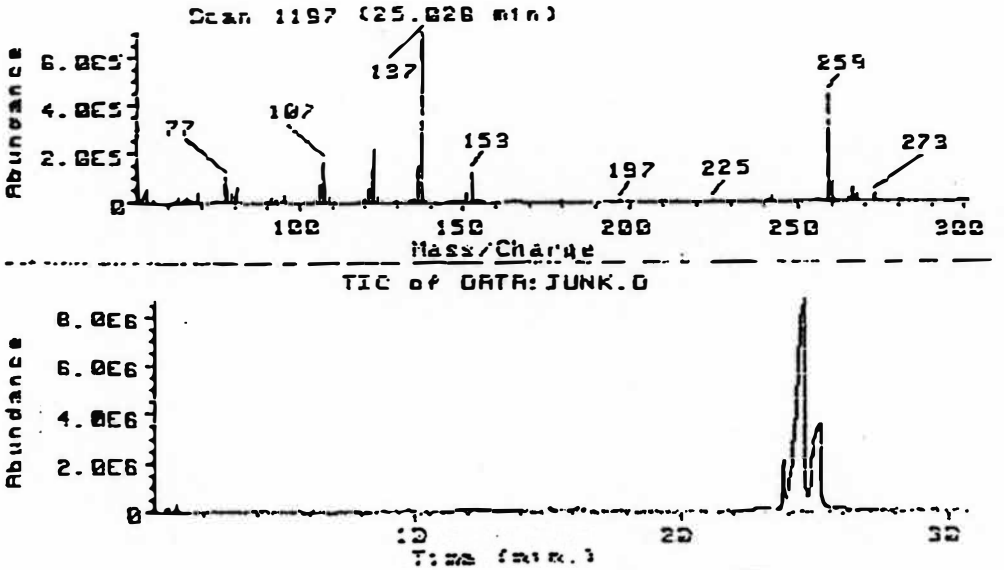


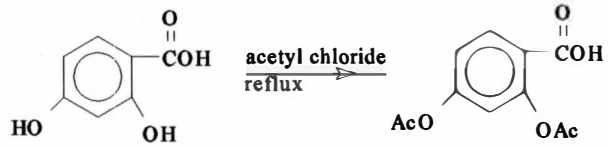
Figure 4. GC-MS of NaOH Hydrolysis on BBr_3 Complex of 2,4-Dimethoxy-N(2-methoxybenzyl)benzamide Sample.

Based on silica and alumina thin layer chromatography, the separation of these compounds by chromatography was not feasible and alternate methods for the

formation of the amide were considered.

Further attempts to cleave the aryl methyl ethers using iodotrimethylsilane or sodium iodide and chlorotrimethyl silane in dry acetonitrile resulted in a mixture of products, the resulting product being an oil which was believed to be a mixture of partially deprotected product. Cleavage with 48% aqueous hydrogen bromide and glacial acetic acid at reflux resulted in decomposition of the amide.

Due to the difficulties associated with cleavage of the aryl methyl ethers, the phenols were protected with methylethyl ethers and acetyl groups in a similar fashion given for the first amide. The reaction scheme for these intermediates is given below in equations 18-21.



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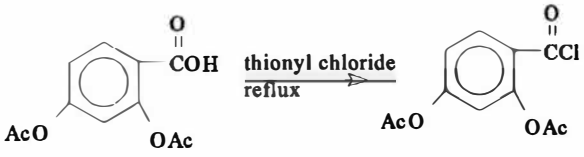

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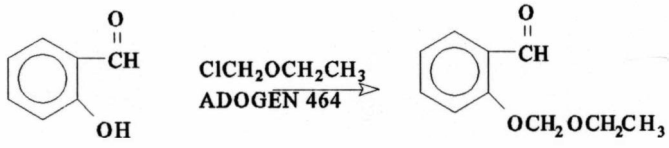
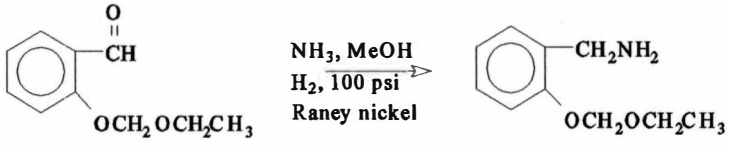


(20)



(21)

For the aldehyde, FTNMR gave peaks at 1.22, 3.74, and 5.33 ppm confirming the presence of the methylethyl ether group. In addition FTIR analysis did not show the broad O-H stretch in the region 3200-3600 cm^{-1}, expected from any unprotected product. Reductive amination of the aldehyde showed the presence of two peaks at 3400 cm^{-1} and 3310 cm^{-1} due to N-H stretching. Theabsence of an aldehyde C=O stretch at 1682 cm^{-1} was taken as evidence of the successful amination of the protected aldehyde. Because these compounds were used in the synthesis of 2,4-dihydroxy-N(2-hydroxybenzyl)benzamide which was proven to be chemically pure, we can infer that 2-ethoxymethoxybenzaldehyde and 2-ethoxymethoxybenzylamine were successfully prepared.

A protected amide intermediate was then formed using 2-ethoxymethoxybenzylamine and 2,4-diacetylbenzoyl chloride using the modified Schotten-Baumann method. A oily liquid was the result of this synthesis and GC-MS results suggested that a mixture of protected and partially protected compound existed, similar to that found for the first amide. Again, instead of isolating the intermediate, the protection groups were hydrolyzed from the oily intermediate under acidic conditions. Workup of the solution gave a white solid with a m.p.=163^{0}C. Spectral data for this compound are given in Tables 13,14,15. The GC-MS gives a molecular ion peak consistent with the deprotected amide. FTIR shows the expected broad O-H stretch with absence of any C=O stretches due to the acetyle protecting groups. FTNMR does not give any signals corresponding to the ether hydrogens, thus

confirming the absence of the methylethyl ether group. Combustion analysis found

Table 13

FTNMR of 2,4-Dihydroxy-N(2-hydroxybenzyl)benzamide
(Acetone-d_6)

δ(ppm)	no. of hydrogens	peak type	assignment	J(Hz)
4.71	2	doublet	methylene	0.03
6.50-7.83	7	singlets	aromatic	
8.66	1	broad	amide	
8.9-9.6	2	broad	phenols	
12.2-12.6	1	broad	phenol	

Table 14

FTIR of 2,4-Dihydroxy-N(2-hydroxybenzyl)benzamide
(KBr pellet)

wavelength cm^{-1}	intensity	assignment
3050-3600	broad, strong	O-H stretch
1646	broad, strong	C=O stretch

Table 15

GC-MS of 2,4-Dihydroxy-N(2-hydroxybenzyl)benzamide
(KBr pellet)

m/z+	fragmentation
259	molecular ion peak
153	$(HO)_2C_6H_3CONH$
137	$(HO)_2C_6H_3CO$
121	$(HO)C_6H_4CH_2$

%C=64.8%, H=5.10%, N=5.36%,O=24.7% which was within experimental error of the theoretical values of %C=64.9%, H=5.06%, N=5.41%, O=24.7%. These results, including the absence of protection groups as indicated by spectral data are evidence for the purity and synthesis of 2,4-dihydroxy-N(2-hydroxybenzyl)benzamide.

Formation of 2-Hydroxy-N(2,4-dimethoxybenzyl)benzamide

An additional amide was prepared in the course of this investigation. 2-hydroxy-N(2,4-dimethoxybenzyl)benzamide was prepared from commercially available *o*-acetylsalicyloyl chloride and 2,4-dimethoxybenzylamine. The acetyl group was then cleaved by reaction with ammonia in methanol, to give the desired amide. Formation of the protected amides and deprotection proceeded smoothly and data for this amide is given in Tables 16,17,18. Again, the GC-MS shows a molecular ion peak consistent with the structure of the deprotected amide. FTIR does not show the C=O stretch due to the acetyl protecting groups. Likewise, FTNMR does not show any signals corresponding to these acetyl groups. Combustion analysis found %C=66.9%, H=5.96%, N=4.87%, O=22.3% which was within experimental error of the theoretical values of %C=67.2%, H=6.00%, N=4.80%, O=22.0%. These results confirm the purity and presence of 2-hydroxy-N(2,4-dimethoxybenzyl)benzamide.

Table 16

FTNMR of 2-Hydroxy-N(2,4-dimethoxybenzyl)benzamide
(DMSO-d_6)

δ(ppm)	no. of hydrogens	peak type	assignment	J(Hz)
3.76	3	singlet	methoxy	
3.83	3	singlet	methoxy	
4.41	2	doublet	methylene	0.03
6.48-7.93	1	multiplets	aromatic	
9.14	1	broad	amide	
12.53	1	broad	phenol	

Table 17

FTIR of 2-Hydroxy-N(2,4-dimethoxybenzyl)benzamide
(KBr pellet)

wavelength cm^{-1}	intensity	assignment
3405	strong	amide N-H stretch
3010	moderate	aromatic C-H stretch
2839	moderate	methyl C-H stretch
1644	strong	C=O stretch
1615	strong	C-N stretch

Table 18

GC-MS of 2-Hydroxy-N(2,4-dimethoxybenzyl)benzamide
(Methanol)

m/z+	fragmentation
287	molecular ion peak
151	$(CH_3O)C_6H_3CH_2$

Table 18—continued

m/z+	fragmentation
121	$(HO)C_6H_4CO$

CONCLUSION

This work demonstrated the difficulty of trying to form an amide directly from unprotected amides. Hydrogen bonding and resonance effects are believed to be the primary cause of these problems. Protection of the phenols by way of aryl methyl ethers does make formation of the intermediates easier, but cleavage of these methyl ethers proves to be very difficult. Formation of intermediates protected with methyl ethyl ethers and acetyl groups is more difficult than the corresponding methyl ether, but cleavage proceeds smoothly and under mild reaction conditions to give the desired amides.

EXPERIMENTAL PROCEDURE

Melting points were determined in open capillary tubes using a Unimelt laboratory device and are uncorrected. Infrared (FTIR) spectra were recorded on a Nicolet 5DXC spectrometer. Nuclear magnetic resonance (FTNMR) were determined on a Bruker 200 MHz instrument. The gas chromatograph used was a Hewlett Packard 5890 series. It has a crosslinked methyl silicone gum column. Attached to the gas chromatograph was a Hewlett Packard 5970 series mass selective detector.

The amines, acid chlorides, and amides were prepared as described.

1. Preparation of Raney Nickel. Sodium hydroxide 190 g (4.75 moles) was dissolved in 750 mL distilled water in a 2 L beaker. The solution was cooled to 10^0C in an ice bath and 150 g of nickel aluminum alloy was added in small portions to keep the temperature below 25^0C. When the mixture was complete, the solution was stirred until hydrogen evolution was complete, and then put on a steam bath over night. The nickel was allowed to settle and the liquid was decanted. The nickel was washed with two 1 liter portions of distilled water and then 250 mL of 10% NaOH. The nickel was washed with distilled water until the decanted liquid was neutral to litmus, and then an additional ten times more. Finally, the nickel was washed with three 100 mL portion of 95% ethanol and then covered with absolute ethanol.

2. Reductive amination of 2,4-dihydroxybenzaldehyde. Absolute ethanol (200

mL) in a 400 mL beaker was tared, transferred to an ice bath and ammonia purged through the solution until an excess of ammonia was dissolved which was determined by reweighing the tared solution. The molar ratio of ammonia to the aldehyde was equal to or greater than five. This solution was transferred to a 2 L Parr Hydrogenation Apparatus, 2,4-dihydroxybenzaldehyde 10 g (0.0710 moles) was added, followed by 5.00 g of Raney Nickel. The reactor was sealed and ammonia was purged through the inlet of the 2 L container for an additional 10 minutes. All valves were closed, stirring was started and the mixture heated to 40^0C at which time hydrogen was added to 100 p.s.i. The reaction was run for three hours, cooled, the Raney nickel filtered, and the ethanol evaporated to 50 mL to give 9.80 g of an oily red solid. After heating on a steam bath, and letting the mixture cool, yellow crystals formed on the bottom of a 150 mL beaker, while an oil floated on top of the ethanol. The oil was decanted and the yellow crystals filtered. These crystals were then recrystallized from ethanol. GC-MS gave several peaks with the following m/z+; 343, 326, 276, 207, 148, 109. The fragmentation for these peaks is consistent with that expected of hydrobenzamides formed from 2,4-dihydroxybenzaldehyde, although no actual compound was isolated.

3. Reaction of 2,4-dihydroxybenzaldehyde with $NaCNBH_3$, (Borch, 1972). 2,4-Dihydroxybenzaldehyde 5.00 g (0.0355 moles) was added to 120 mL absolute ethanol in a 250 mL round bottom flask fitted with a reflux condenser. Ammonium acetate 27.91 g (0.3621 moles) and sodium cyanoborohydride 1.67 g (0.0266 moles)

were added. The reaction was stirred for 24 hours at room temperature. The ethanol was evaporated and then 90 mL distilled water was added to dissolve the solids. The aqueous layer was extracted twice with 50 mL of chloroform and the chloroform evaporated to give a black-tar like oil. This oil was dissolved in 30 mL of 10% sodium hydroxide and stirred 24 hours. The solution was neutralized with 5% HCl, and extracted with chloroform. Evaporation of the solvent gave the same black, tar-like material.

4. Reaction of 2,4-dihydroxybenzaldehyde with K_2CO_3 and chlorodimethyl ether, (Nabaei-Biohenof, 1990). 2,4-Dihydroxybenzaldehyde 5.00g (0.036 moles) was dissolved in 100 mL of dry acetone in a 250 mL three 3 neck flask fitted with a reflux condenser which was maintained under nitrogen purge. Dry potassium carbonate 20 g (0.133 moles) and chlorodimethyl ether 6.12 g (0.071 moles) were then added. The solution was refluxed for 1.5 hour. Undissolved potassium carbonate was filtered, and the acetone evaporated to give a slurry. The slurry was mixed with water and extracted with three 20 mL portions of dichloromethane. The solution was then dried with Na_2SO_4 and evaporated to yield less than 2 mL of liquid. GC-MS analysis gave two peaks r.t.=2 min, 4 min; m/z+=181, 226 corresponding to partially protected and deprotected product. Due to the small yield, this mixture was not separated.

5. Reaction of 2,4-dihydroxybenzaldehyde with sodium hydride and chlorodimethyl ether in DMSO. 2,4-Dihydroxybenzaldehyde 2.00 g (0.0145 moles) was dissolved in 30 mL of DMSO in a 100 mL 3 neck round bottom flask fitted with a

reflux condenser, addition funnel, and was maintained under nitrogen purge. 60% of Sodium Hyride 1.28 g (0.0319 moles) was added slowly. An ice bath was necessary to keep the reaction at room temperature. The solution was stirred for 0.5 hour and then chlorodimethyl ether 11.67 g (0.145 moles) was added dropwise. The solution was stirred for 1 hour and then 200 mL of water was added. The solution was extracted with three 20 mL portions of diethyl ether and the ether was evaporated. The resulting liquid was vacuum distilled at 120-130^{0}C, 5 mm Hg to give a brownish liquid. GC-MS analysis showed a significant amount of DMSO present, and workup of the mixture was discontinued.

6. Reaction of 2,4-dihydroxybenzaldehyde with chlorodimethyl ether, sodium hydride, and 18-Crown-6 Ether, (Ralli, 1976). 2,4-Dihydroxybenzaldehyde 5.00 g (0.036 moles), 18-Crown-6 ether 1.96 g (0.008 moles) were added to 40 mL of diethyl ether. 60% of sodium hydride 3.17 g (0.079 moles) was added to the solution and then chlorodimethyl ether 29.1 g (0.0361 moles). The solution was stirred for 1 hour at reflux, cooled to room temperature, and then filtered to remove any solids. The resulting liquid was dissolved in water and extracted twice with 20 mL portions of diethyl ether. The ether was evaporated to give a white solid. FTIR analysis did not show clear evidence of the protection having occurred, although FTNMR analysis did give some peaks at 1.10 and 3.83 indicating that partial protection may have occured.

7. Formation of 2,4-dimethoxybenzaldehyde. Sodium hydroxide 8 g (0.200 moles) was dissolved in 20 mL ethanol. 2,4-Dihydroxybenzaldehyde 10 g (0.0724

moles) was added to 56 mL ethanol in a 3 neck 250 mL round bottom flask fitted with a reflux condenser and addition funnel. Dimethylsulfate 22.37 g (0.177 moles) was added in alternating portions with the NaOH to the aldehyde mixture. After addition was complete, the reaction was made alkaline with 50% NaOH. The solution was allowed to reflux on a steam bath for 3 hours after which time the solution was cooled and the ethanol evaporated by rotary evaporator. The solution was then extracted two times with 50 mL of diethyl ether. The ether fraction was dried with Na_2SO_4, and evaporated. After recrystallizing in diethyl ether/petroleum ether, white crystals of the product remained. Yield=75%, m.p.=69-70^{0}C,[lit.] m.p.=69-71^{0}C, (Chapman and Hall, 1982).

8. Preparation of 2,4-dimethoxybenzaldhyde oxime. 2,4-Dimethoxybenzaldehyde 25 g (0.150 moles) was dissolved in 75 mL warm ethanol in a 250 mL round bottom 3 neck flask fitted with a reflux condenser. Hydroxylamine hydrochloride 12.5 g (0.180 moles) was dissolved in 15 mL water and transferred to the aldehyde solution and stirred. Sodium hydroxide 9.05 g (0.226 moles) in 13 mL water was added dropwise. The solution was stirred for 1 hour and then saturated with CO_2, at which time a white crystalline solid came out of solution. The solid was filtered and washed with 100 mL distilled water. Further recrystallization in a minimum of hot 95% ethanol gave 2,4-dimethoxybenzaldehyde oxime, yield =72%, m.p.=100-101^{0}C, [lit.] 101.5^{0}C (Chapman and Hall, 1982)

9. Preparation of 2,4-dimethoxybenzylamine. 2,4-Dimethoxybenzaldhyde

oxime 3 g (0.0166 moles) was dissolved in 10 mL 1,2- dimethoxyethane. Sodiumborohydride 2.64 g (0.0697 moles) was added to 40 mL of 1,2-dimethoxyethane in a 250 mL three neck flask fitted with a reflux condenser, addition funnel, and purged with nitrogen. The mixture was cooled to 0^0C and via syringe, titanium tetrachloride 3.83 mL (0.0349 moles) was added to the sodium borohydride mixture. The oxime solution was then added dropwise and the solution was allowed to stir for 14 hours at room temperature. The reaction was quenched with 100 mL distilled water while cooling in ice. The mixture was made alkaline with 28% aqueous ammonia, and then extracted three times with 70 mL portions of benzene. The benzene extracts were washed twice with 50 mL portions of a saturated sodium chloride solution, dried with Na_2SO_4, and the benzene evaporated to give 2,4-dimethoxybenzylamine, yield=31%. The amine was characterized by dissolving in benzene, making acidic with HCl to form the hydrochloride salt of the amine and then was extracted with water. The water was evaporated to 5 mL, the solution allowed to cool and the resulting crystals filtered and washed with 1-3 mL benzene. The crystals were dried over night to give 2,4-dimethoxybenzylamine hydrochloride m.p.=188-189^{0}C,[Lit.] 188-190^{0}C. (Aldrich, 1992)

10. Preparation of 2-methoxy-N(2,4-dimethoxybenzyl)benzamide 2,4-Dimethoxybenzylamine 3.00 g (0.0178 moles) and triethylamine 1.80 g (0.0178 moles) were dissolved in 50 mL dry benzene and transferred to a 100 mL round bottom 3 neck flask fitted with a reflux condenser and addition funnel. The solution

was cooled to 0^0C using an ice bath, and Aldrich *o*-anisoyl chloride 2.90 g (0.0170 moles) was added dropwise. After the addition was complete, the solution was stirred for 1 hour, and then 20 mL of 5% HCl added. The two layers were separated and the benzene fraction washed with an additional 10 mL of distilled water. The benzene was evaporated to give 4.6 g of product as a white viscous liquid., yield=90%. Data for this compound are given in Tables 1,2,3 and are consistent with that expected of the amide.

11. Preparation of 2,4-dimethoxy-N(2-methoxybenzyl)benzamide. 2,4-Dimethoxy-N(2-methoxybenzyl)benzamide was prepared in a similar manner to step 10 using commercially available 2-methoxybenzylamine, triethylamine, and 2,4-dimethoxybenzoyl choride. The yield was 90%, m.p.=89-90^{0}C. GC-MS gave one peak r.t.=12 min., m/z+=301 consistent with that of the desired amide. FTNMR showed the presence of three singlets at 3.83, 3.88, and 3.92 corresponding to the presence of the methoxy groups, and a broad peak at 8.48 corresponding to the amide. FTIR analysis gave a N-H stretch at 3405 cm^{-1}, C-H stretches at 2850 cm^{-1}, and a C=O stretch at 1642 cm^{-1}.

12. Reaction of 2-methoxy-N(2,4-dimethoxybenzyl)benzamide with boron tribromide. 2-Methoxy-N(2,4-dimethoxybenzyl)benzamide 1.68 g (0.0056 moles) was dissolved in 30 mL methylene chloride in a 3 neck 100 mL round bottom flask maintained under nitrogen atmosphere and fitted with a reflux condenser and two rubber septa. The mixture was cooled to -28^{0}C using a dry ice/2-propanol bath and

boron tribromide 3.5 mL (0.037 moles) was added via syringe. The ice bath was removed and upon warming, a white solid came out of solution. 30 g of ice was added to the mixture slowly, and the mixture was filtered. The white solid was then washed with distilled water and methylene chloride, and dried under vacuum at 78^{0}C at 5 mm Hg pressure, yield=105%, m.p.<245^{0}C decomposes. Spectral data for this compound are given in tables 4,5,6. This solid is believed to be a boron tribromide complex of the deprotected amide based on the combustion analysis which gave 8.5% residue. The solid, 1.0 g (1.9 moles) was dissolved in 10 mL 20% of NaOH. The solution was stirred for one week at room temperature, and then acidified with 10% HCl. After washing with water and dichloromethane, GC-MS gave two peaks r.t.=12 min, 22 min; m/z+=137 and 121, 259. No attempt was made to separate these two compounds.

13. Reaction of 2,4-dimethoxy-N(2-methoxybenzyl)benzamide with boron tribromide and hydrolysis using NaOH. 2,4-Dimethoxy-N(2-methoxybenzyl)benzamide (step 11) was reacted with boron tribromide and sodium hydroxide in a similar fashion to that found in step 12. Reaction with NaOH led to complete conversion of the boron-tribromide amide complex to deprotected and partically deprotected amides as indicated by GC-MS in Figure 4, r.t. 10.1, 22 mins, m/z: 259, 273. Based on silica and alumina t.l.c. results, no attempts were made to separate these products by chromatography.

14. Reaction of 2,4-dimethoxy-N(2-(methoxybenzyl)benzamide with sodium

iodide and chlorotrimethylsilane, (Olah, 1979). 2,4-Dimethoxy-N(2-methoxybenzyl)benzamide 1.00 g (0.00366 moles) was dissolved in 50 mL dry acetonitrile in a 3 neck 100 mL round bottom flask purged with nitrogen, and fitted with a reflux condenser and rubber septums. Dry sodium iodide 2.74 g (0.0183 moles) was added, stirred and chlorotrimethylsilane 2.32 mL (0.0183 moles) added via syringe. The reaction was monitored by t.l.c. and did not show disappearance of the starting material after one week. Water was added to hydrolyze the silyl ethers, the acetonitrile evaporated and ether was added and the two layers separated. The etheral layer was washed with water, dried with Na_2SO_4 and evaporated. GC-MS analysis of the resulting product showed a mixture of protected and partially deprotected product. Attempts to increase the reaction rate by heating to reflux gave spectral data inconsistent with the amides.

15. Reaction of 2,4-dimethoxy-N(2-methoxybenzyl)benzamide with 48% HBr in glacial acetic acid, (Rolla, 1978). 2,4-Dimethoxy-N(2-methoxybenzyl)benzamide 1.00 g (0.00366moles) was dissolved in 30 mL glacial acetic acid in a 100 mL round bottom flask fitted with a reflux condenser. 48% Aqueous hydrobromic acid 3.09 g (0.0183moles) was added and the solution heated to reflux. After 24 hours, the mixture was cooled, the solution was diluted to 200 mL with distilled water and extracted twice with 50 mL portions of ether. Evaporation of the ether gave a charred, black solid. Analysis by GC-MS did not give any peaks corresponding to that of the amide and workup was discontinued.

16. Preparation of 2,4-diethoxymethoxybenzylaldehyde using Adogen 464, (Heerdan, 1978). 2,4-Dihydroxybenzaldehyde 4.16 g (0.0295 moles) was dissolved in 25 mL dichloromethane. Sodium hydroxide 2.65g (0.0662 moles) was dissolved in 25 mL distilled water, mixed with the aldehyde solution, and stirred for 15 minutes. Adogen 464, 1.0 g (0.003 moles) was added and stirred for 15 minutes. Chloromethylethyl ether 8.54 g (0.0903 moles) was added dropwise and the reaction stirred for 1 hour. The layers were separated and the organic fraction adsorbed on to an alumina column. The product was flashed through the column using hexane and ethyl acetate, to give 3.79 g 2,4-di(ethoxymethoxy)benzaldehyde, yield=57%. Spectral data for this liquid are given in Tables 19, 20 and are consistent with protection of the aldehyde.

17. Preparation of 2,4-Diethoxymethoxybenzaldehyde in DMF. 2,4-Dihydroxybenzaldehyde 5.00 g (0.0362 moles) was dissolved in 50 mL DMF in a 100 mL 3 neck flask fitted with a reflux condenser and purged with nitrogen. 60% of Sodium hydride 3.19 g (0.0796 moles) was added slowly and the mixture allowed to stir for 0.5 hour. Chloromethylethyl ether 6.41 g (0.0796 moles) was added slowly to the solution via syringe. After addition was complete, the mixture was heated to 60-80^{0}C and stirred for 1.5 hours after which time the solution was cooled and 200 mL water was added. The mixture was transferred to a 500 mL separatory funnel and extracted with three 50 mL portions of diethyl ether. The diethyl ether was evaporated and the resulting solution distilled at 5 mm Hg 150-160^{0}C to give 51% of

Table 19

FTNMR of 2,4-Diethoxymethoxybenzaldehyde
($CDCl_3$)

δ(ppm)	no. of hydrogens	peak type	assignment	J(Hz)
1.22	6	triplet	methyls	0.02-0.03
3.74	4	multi	methylene	
5.26,5.32	4	singlets	methylene	
6.77-7.88	3	doublet	aromatic	
10.5	1	singlet	aldehyde	

Table 20

FTIR of 2,4-Diethoxymethoxybenzaldehyde
(NaCl plate)

wavelength cm^{-1}	intensity	assignment
2978	strong	CH_3 stretching
2902	strong	CH_2 stretching
2887	strong	C-H stretch of aldehyde
2750	moderate	C-H stretch of aldehyde
1682	strong	aldehyde C=O stretch

2-ethoxymethoxybenzaldehyde. Spectral data was similar to that found using the Adogen 464 method given above.

18. Preparation of 2-Ethoxymethoxybenzaldehyde. 2-Ethoxymethoxybenzaldehyde was prepared in a similar manner to step 16 above using salicylaldehyde 5.00 g (0.0409 moles), sodium hydroxide 1.80 g (0.045 moles), Adogen 464 1.0 g (0.003 moles) , and chloromethylethyl ether 8.5 g (0.0899 moles).

A typical yield was 60-89%. Spectral data are given in Tables 21, 22.

Table 21

FTNMR of 2-Ethoxymethoxybenzaldehyde
($CDCl_3$)

δ(ppm)	no. of hydrogens	peak type	assignment	J(Hz)
1.22	3	triplet	methyl	0.03
3.74	2	quartet	methylene	0.02
5.33	2	singlet	methylene	
7.22-7.90	1	multiplet	aromatic	0.04
10.5	1	singlet	aldehyde	

Table 22

FTIR of 2-Ethoxymethoxybenzaldehyde
(NaCl plate)

wavelength cm^{-1}	intensity	assignment
3050	strong	aromatic C-H stretch
2950	moderate	methyl C-H stretch
2880	moderate	methylene C-H stretch
2850	moderate	O-CH_2-O, C-H stretch
2750	moderate	aldedehyde C-H stretch
1682	strong	aldehyde C=O stretch

19. Preparation of 2-ethoxymethoxybenzaldehyde in DMF. 2-Ethoxymethoxybenzaldehyde was prepared in a similar fashion to step 17 above using 60% of Sodium hydride 1.92 g (0.0481moles) and chloromethylethyl ether 4.26 g (0.0441 moles). The product distilled at 120-130^{0}C at 5 mm Hg pressure to yield 63%

2-ethoxymethoxybenzaldehyde. Spectra for the compound were similar to that found using the phase transfer method.

20. Preparation of 2,4-(diethoxymethoxy)benzylamine. Ammonia was purged through 400 mL dry methanol for 1 hour in a 2 L parr hydrogenation apparatus. Raney nickel 5 g and 2,4-di(ethoxymethoxy)benzaldehyde 6.12 g (0.0275 moles) was added. The reactor was sealed and purged an additional 10 minutes with ammonia. The autoclave was then heated to 45^{0}C, hydrogen was added to 100 p.s.i. and the reaction run for three hours. The mixture was cooled, vented, and the solution filtered through cellite to remove Raney nickel. The ethanol was evaporated and 2,4-diethoxymethoxybenzylamine vacuum distilled at 135-140^{0}C, 5 mm Hg pressure. Yield=45%. Spectral data for this compound are given in Tables 23,24. Because 2-hydroxy-N(2,4-dihydroxybenzyl)benzamide was successfully prepared and was proven to be chemically pure, it can be deduced that 2,4-diethoxymethoxybenzaldehyde and 2,4-diethoxymethoxybenzylamine were successfully prepared.

21. Preparation of 2-ethoxymethoxybenzylamine. 2-Ethoxymethoxybenzylamine was prepared in a similar manner to step 20 above using 2-ethoxymethoxybenzyaldehyde 9.34 g (0.0516 moles), ammonia, Raney nickel 5 g and 500 mL dry methanol. The yield was 82% after vacuum distillation at 120-125^{0}C at 5 mm Hg. Spectral data for this compound are given in Tables 25,26.

22. Preparation of 2,4-diacetylbenzoic acid. 2,4-Dihydroxybenzoic acid 25 g (0.162 moles) was added to 60 mL (0.849 moles) of acetyl chloride in a 100 mL

Table 23

FTNMR of 2,4-Di(ethoxymethoxy)benzylamine
($CDCl_3$)

δ(ppm)	no. of hydrogens	peak type	assignments	J(Hz)
1.22	6	triplet	methyl	0.02-0.03
1.5-1.7	2	2	broad	amine
3.74	6	multi	methylene	
5.26.5.32	4	singlet	methylene	
6.69-7.10	1	multiplets	aromatic	

Table 24

FTIR of 2,4-Di(ethoxymethoxy)benzylamine
(NaCl Plate)

wavelength cm^{-1}	intensity	assignment
3400	moderate	N-H stretch
3310	moderate	N-H stretch
2978	strong	methyl C-H stretch
2962	strong	methylene C-H stretch
1605	strong	C-N stretch

Table 25

FTNMR of 2-Ethoxymethoxybenzylamine
($CDCl_3$)

δ(ppm)	no. of hydrogens	peak type	assignment	J(Hz)
1.18	3	triplet	methyl	0.02
1.8-2.5	2	broad	amine	
3.63	4	broad	methylenes	
5.24	2	singlet	methylene	

Table 25—continued

δ(ppm)	no. of hydrogens	peak type	assignment	J(Hz)
6.93-7.31	4	multitet	aromatic	

Table 26

FTIR of 2-Ethoxymethoxybenzylamine
(NaCl plate)

wavelength cm^{-1}	intensity	assignment
3378	weak	primary N-H stretch
3304	weak	primary N-H stretch
2977	moderate	methyl C-H stretch
2930	moderate	methylene C-H stretch

round bottom flask fitted with a reflux condenser. The solution was refluxed for 4 hours, cooled to room temperature, and allowed to crystallize overnight. The solids were filtered from the excess acetyl chloride and washed with diethyl ether until white. No further purification was necessary. Yield=81%, m.p.=136^{0}C, $^{Lit.}$m.p.= 136^{0}C (Byatnal, 1952).

23. Preparation of 2,4-diacetylbenzoyl chloride. 2,4-Diacetylbenzoyl chloride was prepared accordig to a known procedure (Byatnal, 1952). 2,4-Diacetylbenzoic acid 10 g (0.0424 moles) was added to 98% thionyl chloride 15 mL (0.202 moles) in a 100 mL round bottom flask fitted with a reflux condenser. The solution was refluxed for 3 hours, the excess thionyl chloride removed by vacuum. The yield was

quantitative.

24. Preparation of 2-hydroxy-N(2,4-dihydroxybenzyl)benzamide. 2,4-Diethoxymethoxybenzylamine 0.78 g (0.0031 moles) and triethylamine 0.34 g (0.0034 moles) was dissolved in 50 mL methylene chloride and transferred to a three neck 100 mL round bottom flask fitted with a reflux condenser and addition funnel. The solution was cooled to 0^0C and Aldrich *o*-acetylsalicyloyl chloride 0.61g (0.0031moles) in 20 mL methylene chloride was added dropwise. The solution was stirred for 1 hour at room temperature and then 20 mL of 5% HCl was added and the layers were separated. The organic fraction was washed with 10 mL of distilled water, dried with Na_2SO_4, and the methylene chloride evaporated. The resulting oil was dissolved in 20 mL methanol and 5 mL of 15% HCl was added. The solution was stirred 24 hours, the methanol was evaporated, and the resulting yellow solid recrystallized from ethanol and water. The solid was dried under vacuum at room temperature, 5 mm Hg, to give 0.5 g 2-hydroxy-N(2,4-dihydroxybenzyl)benzamide. Yield=63%, m.p.<50^0C decomposes. Combustion analysis found C=65.1%, H=5.11%, N=5.6%, O=24.2%; known C=64.9%, H=5.06%, N=5.41%, O=24.7%. Spectral data for this compound and assignments are given in Tables 7,8,9.

25. Preparation of 2,4-dihydroxy-N(2-hydroxybenzyl)benzamide. 2,4-Dihydroxy-N(2-hydroxybenzyl)benzamide was prepared in a similar fashion to step 24 above. 2-Ethoxymethoxybenzylamine 3.62 g (0.020 moles), triethylamine 2.02 g (0.020 moles), and 2,4-diacetylbenzoyl chloride 4.65 g (0.0182 moles) were stirred

for 1.5 hours in methylene chloride. 30 mL of water was added and the organic fraction separated and washed with an additional 30 mL water, and then twice with 30 mL portions of 5% HCl. The methylene chloride was evaporated and the resulting oil dissolved in 20 mL methanol. A white solid came out of solution which was then filtered, washed with three 5 mL portions of cold methanol. The resulting solid was dissolved in 70 mL luke warm methanol and 3 mL of concentrated hydrochloric acid added. The solution was stirred for 2 hours, the methanol evaporated and the solid extracted into diethylether and washed with water. Evaporation of the ether gave a pale brown solid which upon recrystallization from ethanol and water gave a white solid, m.p.=163^{0}C, yield=57%. Combustion analysis found C=64.8%, H=5.10%, N=5.36%, O=24.7% (by difference); known C=64.9%, H=5.06%, N=5.41%, O=24.7%. Spectral data for this compound are characterized in Tables 13, 14, 15.

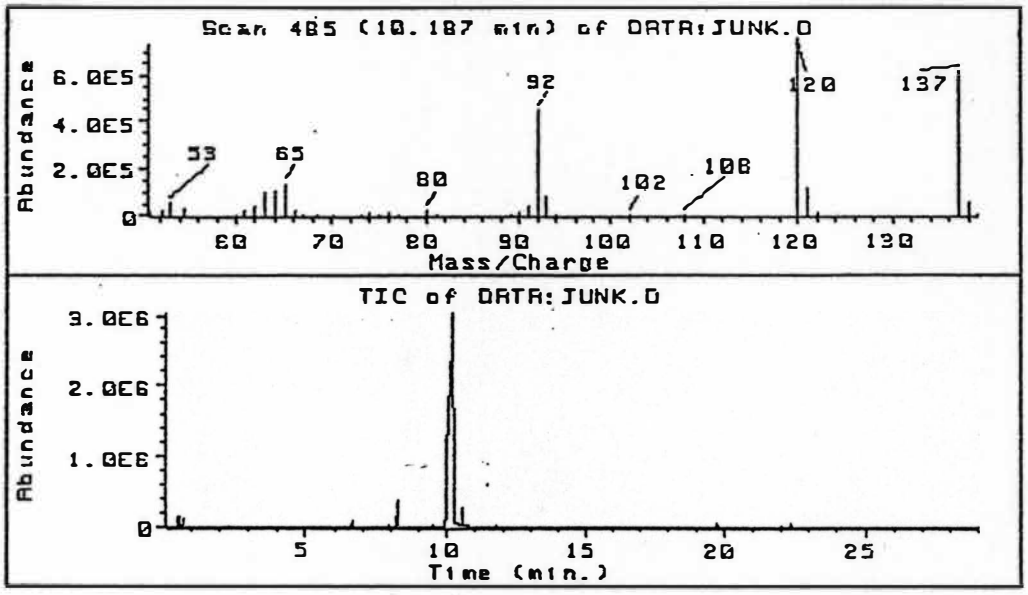
26. Preparation of 2-hydroxy-N(2,4-dimethoxybenzyl)benzamide. 2-Hydroxy-N(2,4-dimethoxybenzyl)benzamide was prepared in a similar manner to step 24 above. *O*-Acetylsalicyloyl choride, 2,4-dimethoxybenzylamine, and triethylamine were reacted together using the modified Schotten-Baumann reaction. The resulting white solid was not isolated because partial hydrolysis of the acetyl groups may have occured during the acid wash in a similar manner found for the previous amides. This white solid was dissolved in methanol and ammonia was passed through the solution for two hours while stirring. The methanol was evaporated, the resulting solid taken up in ether, and washed with water. Evaporation of the solvent gave 90% yield of the

deprotected amide, m.p.=89-90^{0}C. Elemental analysis: calculated %C=67.9, H=5.96, N=4.87, O=22.3; Found %C=67.2, H=6.00, N=4.80, O=22.0. Spectral data are given in Tables 16, 17, 18.

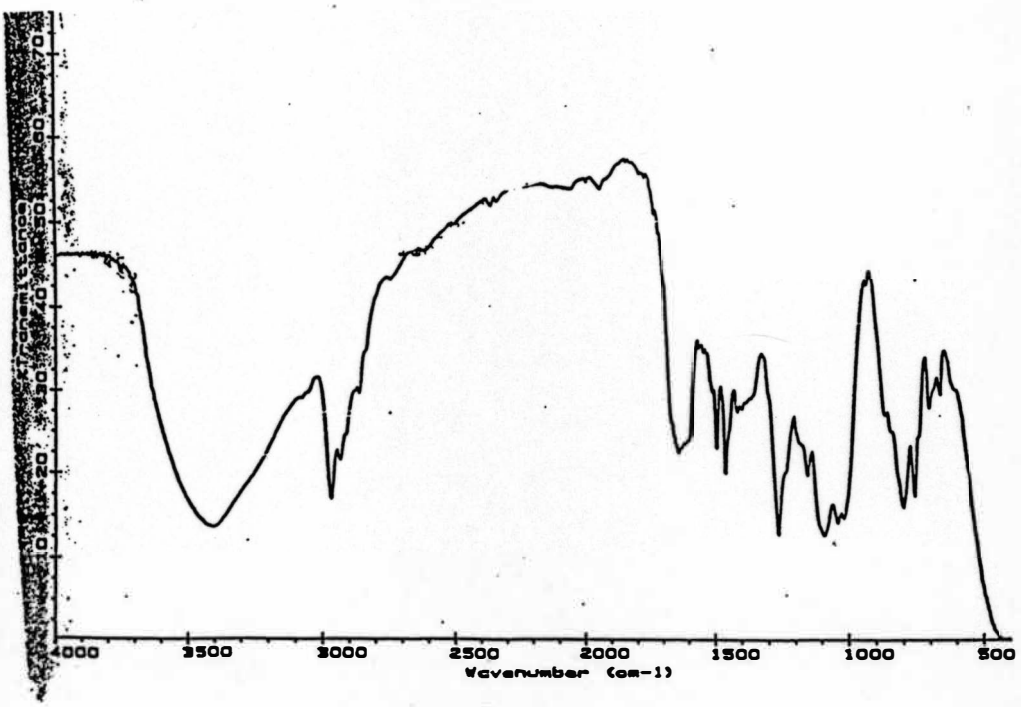
Appendix A

Spectral Data

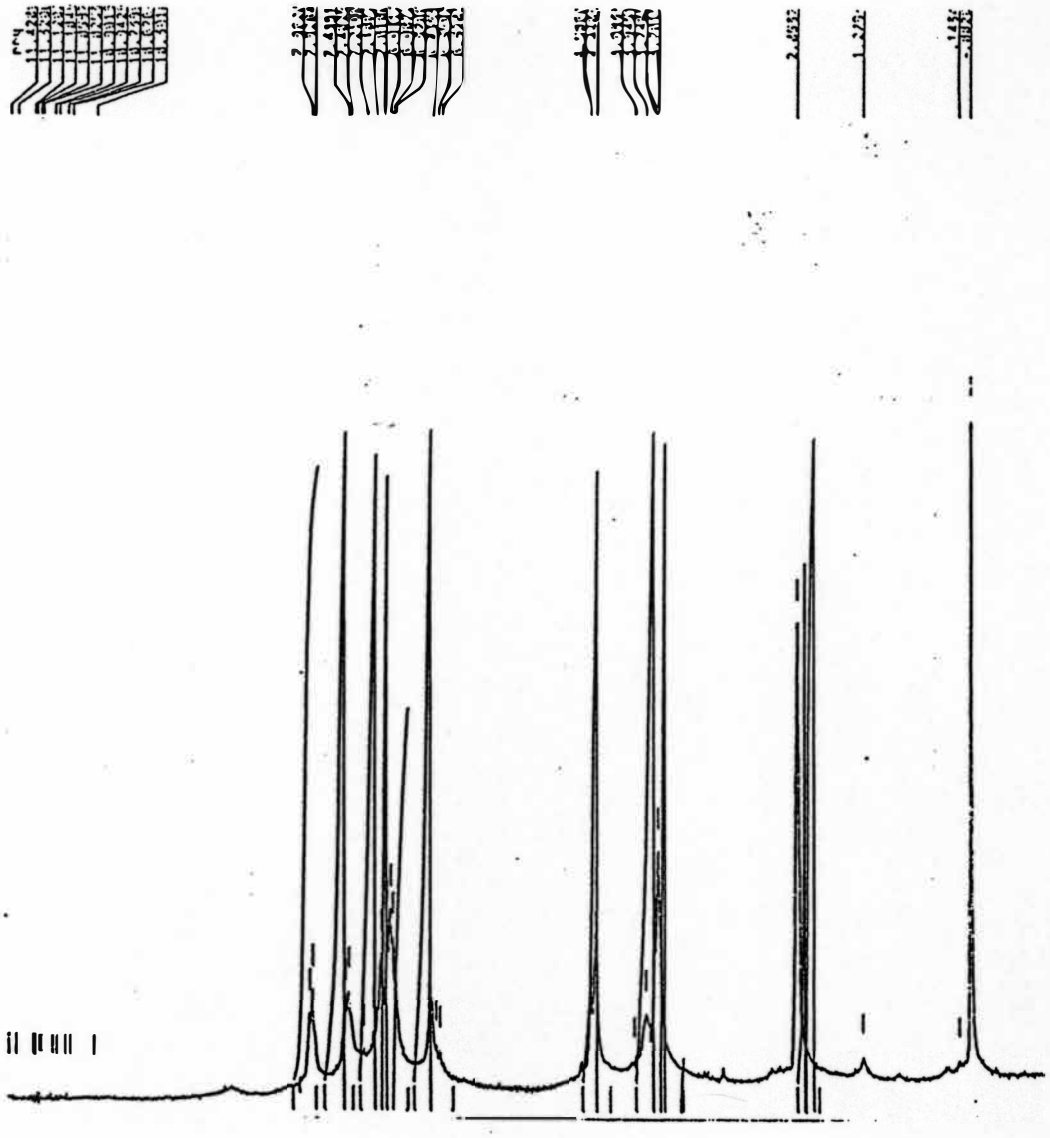
GC-MS of 2-Hydroxy-N(2,4-dihydroxybenzyl)benzamide



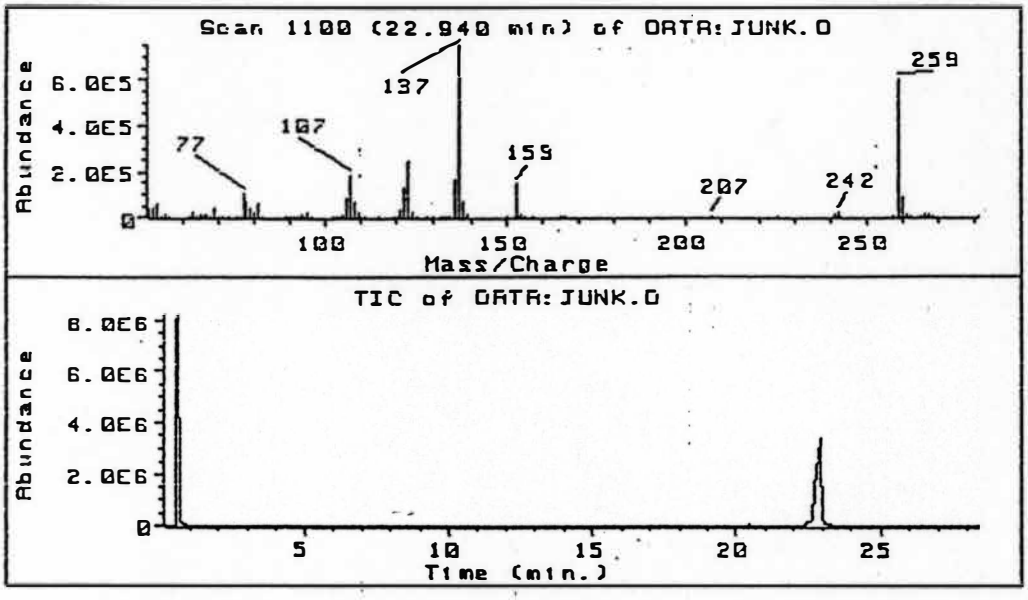
FTIR of 2-Hydroxy-N(2,4-dihydroxybenzyl)benzamide



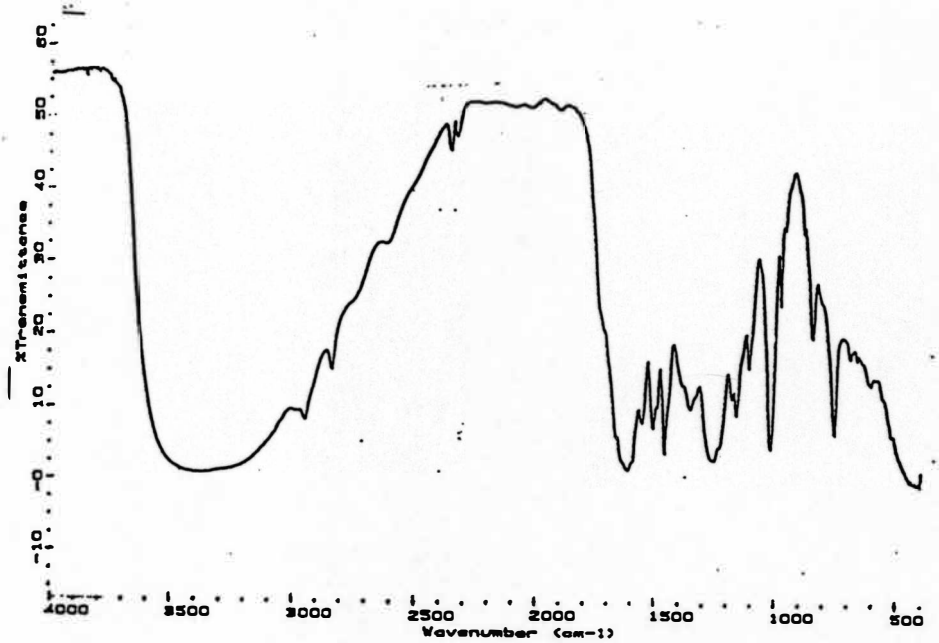
FTNMR of 2-Hydroxy-N(2,4-dihydroxybenzyl)benzamide



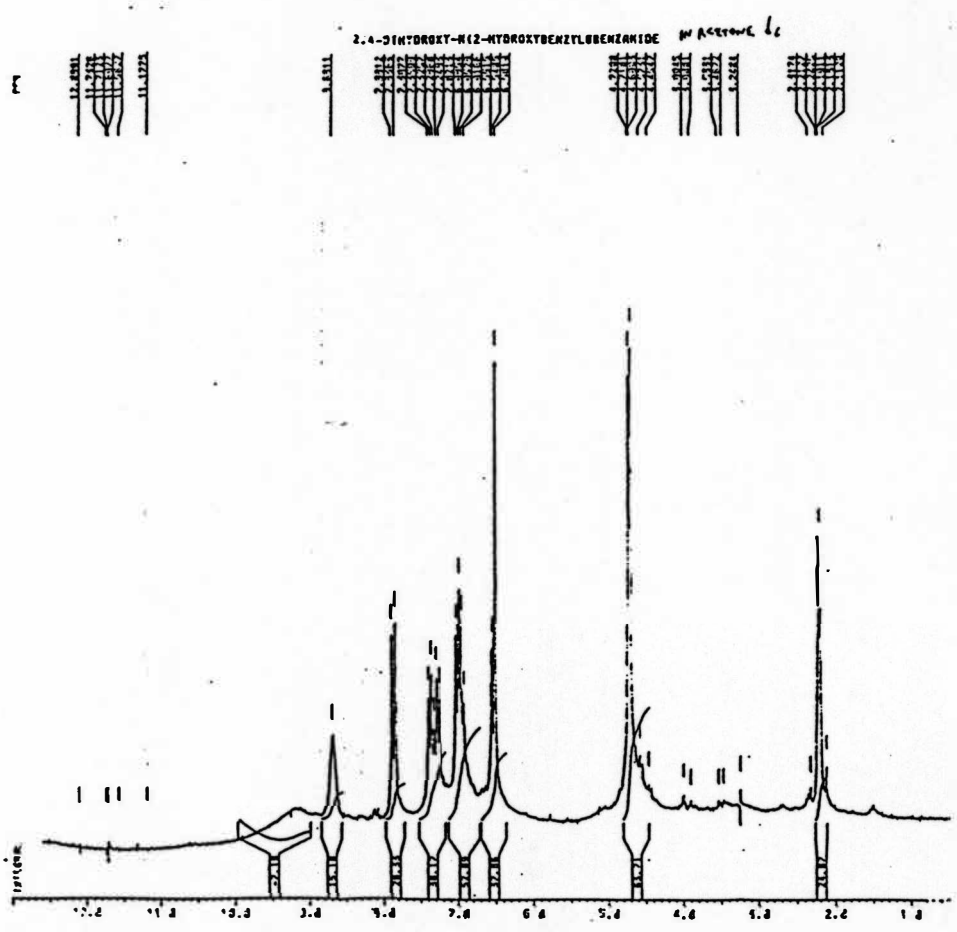
GC-MS of 2,4-Dihydroxy-N(2-hydroxybenzyl)benzamide



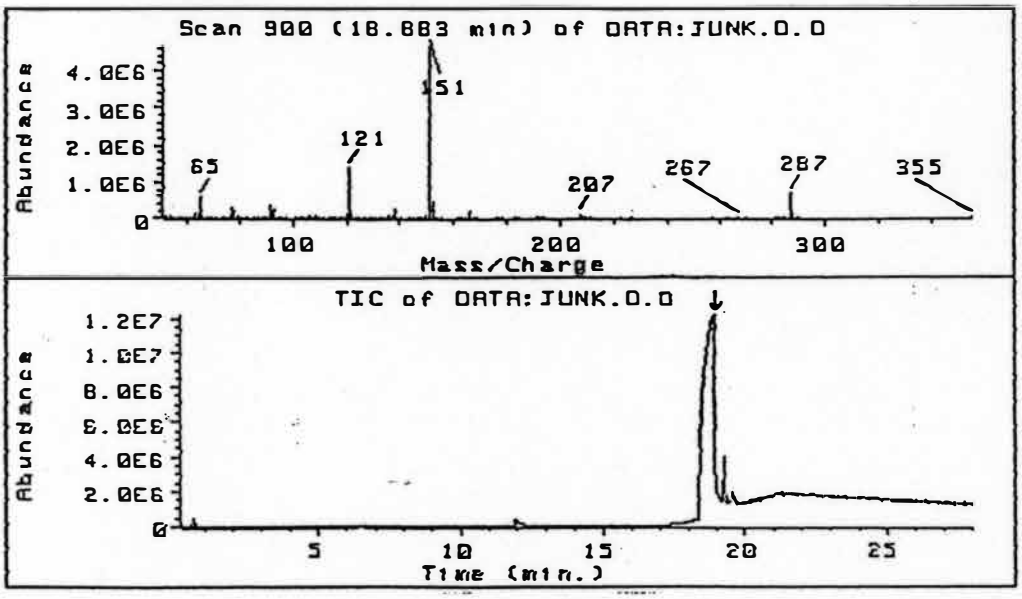
FTIR of 2,4-Dihydroxy-N(2-hydroxybenzyl)benzamide



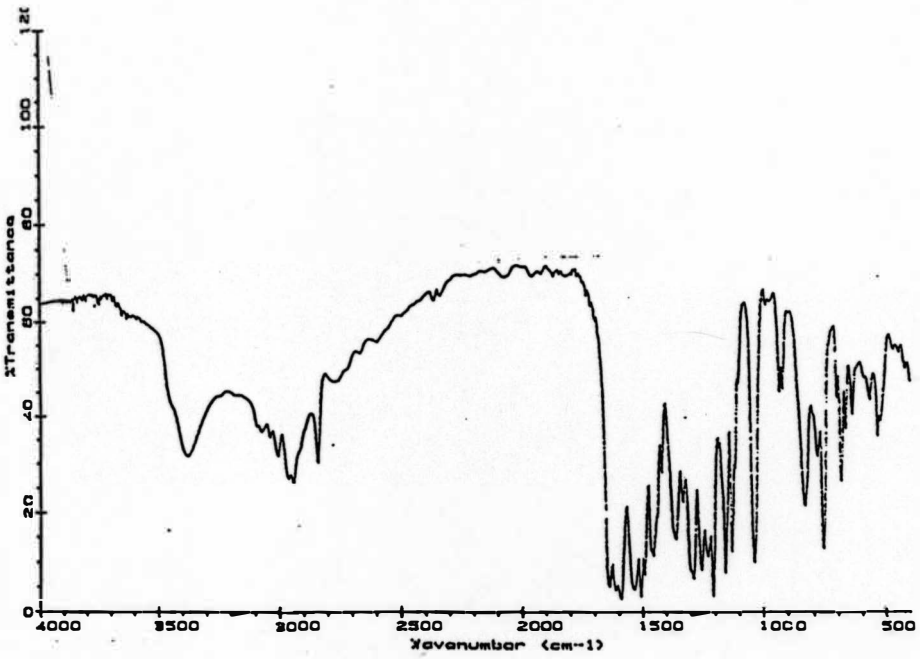
FTNMR of 2,4-Dihydroxy-N(2-hydroxybenzyl)benzamide



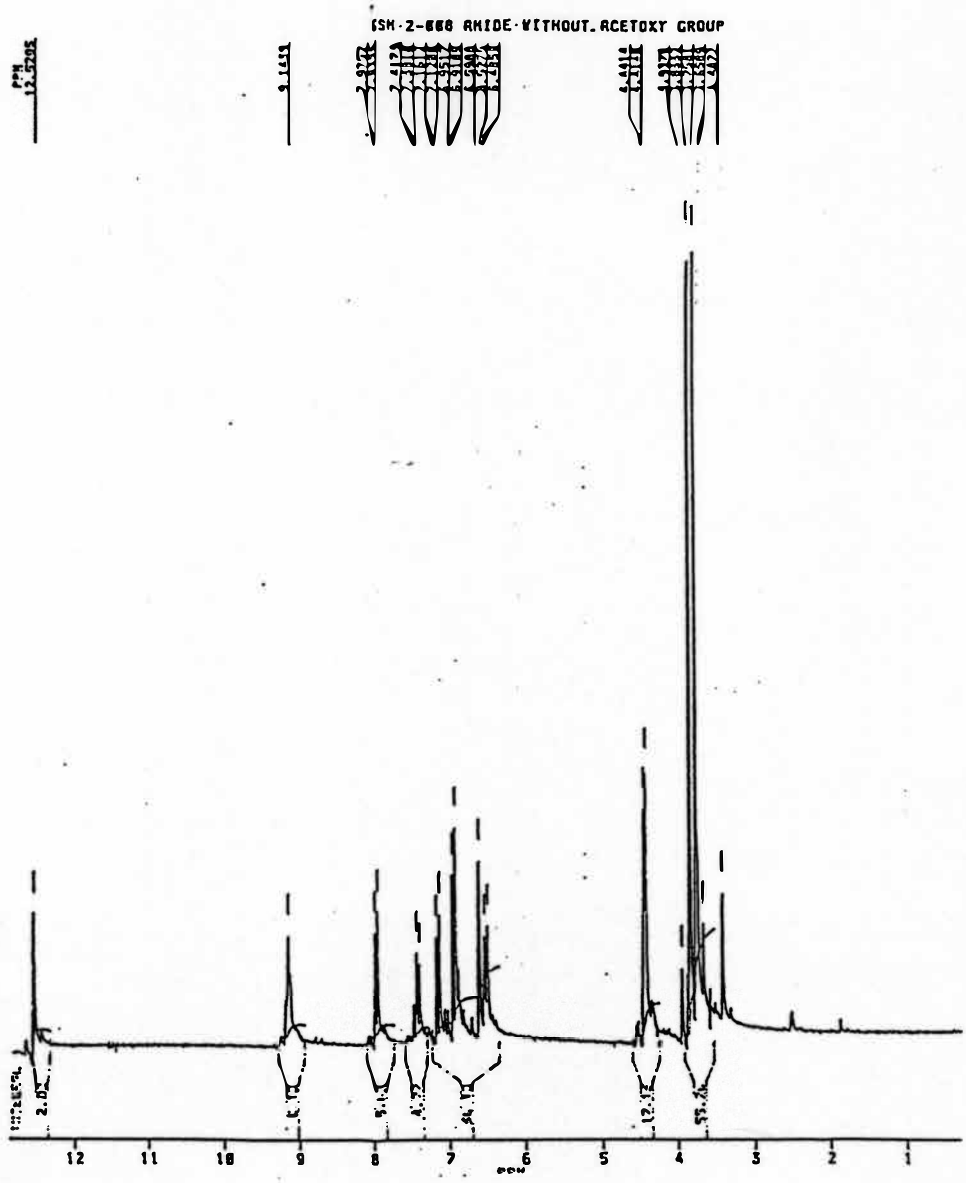
GC-MS of 2-Hydroxy-N(2,4-dimethoxybenzyl)benzamide



FTIR of 2-Hydroxy-N(2,4-dimethoxybenzyl)benzamide



FTNMR of 2-Hydroxy-N(2,4-dimethoxybenzyl)benzamide



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