Article

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o-Hydroxylaminobenzaldehydes and the *N*-Acylated Derivatives Thereof

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Dedicated to the memory of Dr. Raymundo Cruz Almanza, a distinguished organic chemist, a true patriot, and a steadfast friend.

Abstract. Ethyl acetate solutions of *o*-hydroxylaminobenzaldehydes (**1a**, **8c**, **8d**) can be generated by reduction of the corresponding nitro compounds with zinc and ammonium chloride in a two phase ethyl acetate-water system at room temperature, but 2-nitro-3,6-dimethoxybenzaldeyhde (**4b**) is converted into the anthranil **11** under these conditions. The *N*-acylated compounds derived from **1a** and **8c** exist exclusively as the cyclic tautomers (**6a-c** and **9a**) in solution and in the solid state, whereas the *N*-acetyl compound **9b** is in equilibrium with the open chain form **10** in solution, but only the cyclic form is present in the solid state. The *N*-acylated-*o*-hydroxylaminobenzaldehydes undergo a novel internal redox reaction on thermolysis generating *o*-acylaminobenzoic acids which are converted into 2-substituted-4H-3,1-benzoxazin-4-ones (e.g., **6b**→**12b**→**13b**) to a greater or lesser extent under the reaction conditions.

Keywords: *O*-hydroxyaminobenzaldehydes, reduction, anthranil, *N*-acyl, benzoxozinones.

Resumen. Soluciones de *o*-hidroxilaminobenzaldehídos (**1a**, **8c**, **8d**) en acetato de etilo se pueden generar por medio de la reducción del correspondiente compuesto nitro con zinc y cloruro de amonio en un sistema bifásico de acetato de etilo-agua a temperatura ambiente, sin embargo, el 2-nitro-3,6-dimetoxibenz-aldehido (**4b**) se convierte en el antralino **11** bajo estas condiciones. Los compuestos *N*-acilados derivados de **1a** y **8c** existen exclusivamente como los tautómeros cíclicos (**6a-c** y **9a**) en solución y en el estado sólido, mientras que el compuesto *N*-acetilo **9b** esta en equilibrio con la forma abierta **10** en solución, pero solo la forma cíclica está presente en el estado sólido. Los *N*-acilados *o*-hidroxil- aminobenzaldehídos sufren una nueva reacción oxidoreductiva interna bajo termólisis generando ácidos *o*-acilaminobenzóicos los cuales son convertidos en 2-substituidos-4H-3,1-benzoxazin-4-onas (e.g., **6b**→**12b**→**13b**) en mayor o menor grado, bajo las condiciones de reacción.

Palabras clave: *O*-hidroxiaminobenzaldehídos, reducción, antranilo, *N*-acilo, benzoxazinones.

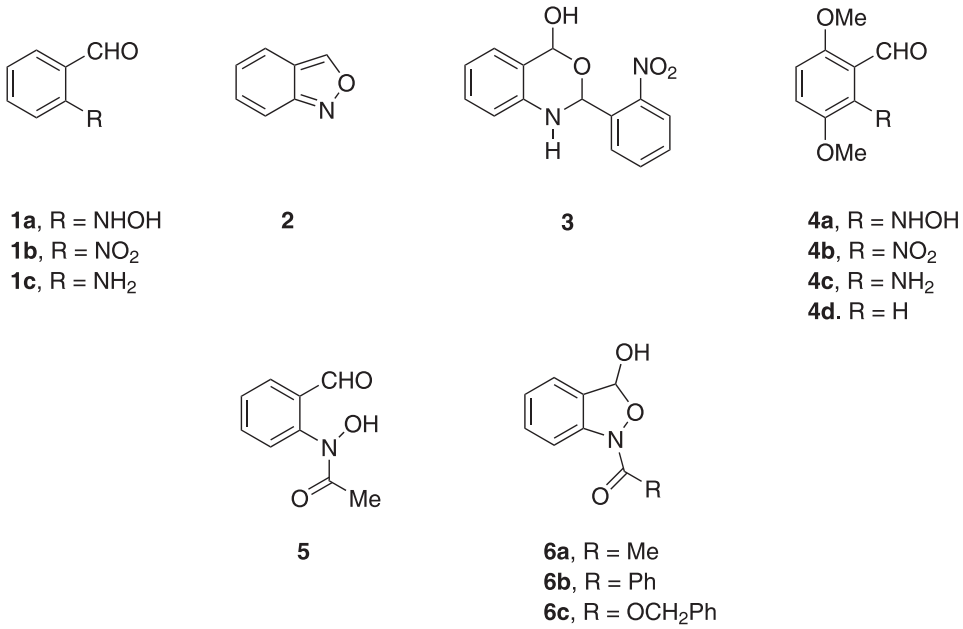
Introduction

o-Hydroxylaminobenzaldehydes and/or the *N*-acylated derivatives thereof were required as intermediates for another study. Pure *o*-Hydroxylaminobenzaldehyde (**1a,** Scheme 1) itself has never been isolated, but its existence as an intermediate during the reduction of *o*-nitrobenzaldehyde (**1b**) to anthranil (**2**) [1] or to the so-called agnotobenzaldehyde (**3**) [2], the precise structure of which is not known [3], is secure. Furthermore, the presence of **1a** in solution during controlled potential reduction of **1b** is well documented [4]. The only other *o*-hydroxylaminobenzaldehyde derivative for which data exists in the literature is the dimethoxy compound **4a**, which remarkably was reported [5] to be a stable, crystalline, solid generated by the catalytic reduction of the corresponding nitro compound **4b**.

The *N*-acetyl derivative **5** is the sole *N*-acylated o-hydroxylaminobenzaldehyde described to date. This compound was first obtained by Bamberger [2] as one of the products of the acetylation of agnotobenzaldehyde with acetic anhydride, and was subsequently shown by Bakke and Engan [3] to exist in the cyclic form **6a**.

Results and Discussion

Given the fragile nature of *o*-hydroxylaminobenzaldehyde, it was assumed that all congeners of this compound would have a similar lack of stability, the reported [5] robust nature of **4a** notwithstanding. Therefore, a very mild procedure for the reduction of aryl nitro compounds to arylhydroxylamines was devised using nitrobenzene (**7a**, Scheme 2) as a model system. The process was based on the use of the well known zinc/ammonium chloride combination for the reduction of aromatic nitro compounds to hydroxylamines [6], except that the reaction was effected at room temperature in a two phase ethyl acetate-water system. Under these conditions overreduction to aniline was minimized and pure phenylhydroxylamine (**7b**, Scheme 2) was isolated in at least 75 % yield, after a reaction time of *ca* 5 h. When these conditions were applied to *o*-nitrobenzaldehyde, TLC (thin layer chromatography) showed that the nitro compound disappeared rapidly (< 2 h) and was replaced by a major, more polar material. Rapid removal of the solvent from an aliquot of the organic phase *in vacuo* below room temperature, and immediate measurement of the NMR spectrum of the residue, showed that a mixture contain-



1a, R = NHOH
1b, R = NO_2
1c, R = NH_2

2

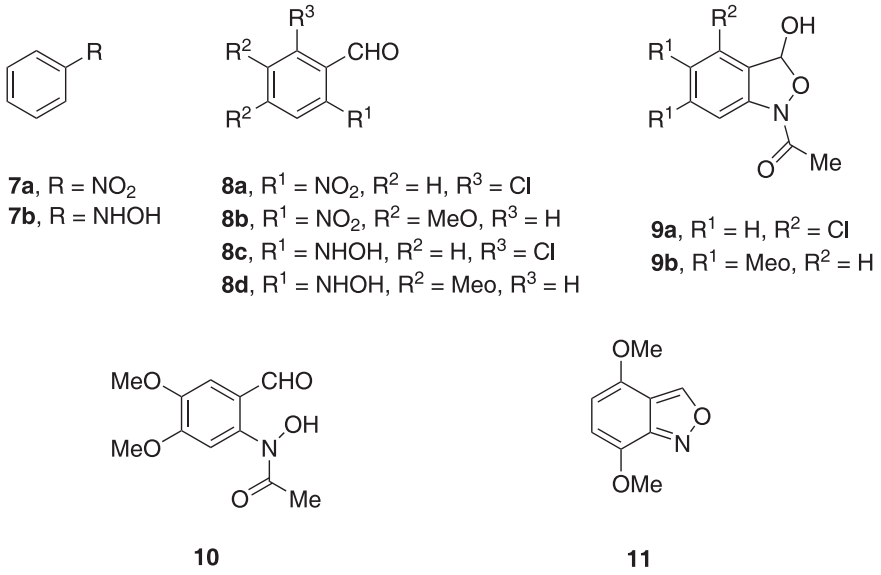
3

4a, R = NHOH
4b, R = NO_2
4c, R = NH_2
4d. R = H

5

6a, R = Me
6b, R = Ph
6c, R = OCH_2Ph

Scheme 1



7a, R = NO_2
7b, R = NHOH

8a, R^1 = NO_2, R^2 = H, R^3 = Cl
8b, R^1 = NO_2, R^2 = MeO, R^3 = H
8c, R^1 = NHOH, R^2 = H, R^3 = Cl
8d, R^1 = NHOH, R^2 = Meo, R^3 = H

9a, R^1 = H, R^2 = Cl
9b, R^1 = Meo, R^2 = H

10

11

Scheme 2

ing **1a** (65.5 %), **1b** (7 %), 2-amino-benzaldehyde (**1c**, 5.5 %), and anthranil (**2**, 21.5 %) was obtained. Ethyl acetate solutions of **1a** could be kept for several days at 5 ºC without significant deterioration, but a neat sample left at room temperature for *ca* 12 h had undergone substantial dehydration to anthranil (50 %) and < 30 % of the hydroxylamino compound remained.

Although the utilization of **1a** as such for synthetic purposes was not practical, the ethyl acetate solutions thereof functioned reasonably well in this respect. For example, *N*-acylation could be effected with acyl halides in the presence of aqueous sodium bicarbonate at *ca* – 5 ºC [7]. The N-acetyl (**6a**), *N*-benzoyl (**6b**), and *N*-benzyloxycarbonyl (**6c**) derivatives were prepared in this way in 52 %, 45-53 %, and 21 % yields, respectively. As judged from the NMR and IR spectra, these compounds exist in the cyclic forms **6a-c** to an extent of at least 95 % both in solution (DMSO) and in the solid state. This methodology could also be used to prepare the *N*-acetyl compounds **9a** and **9b** from the nitro compounds **8a** and **8b**.

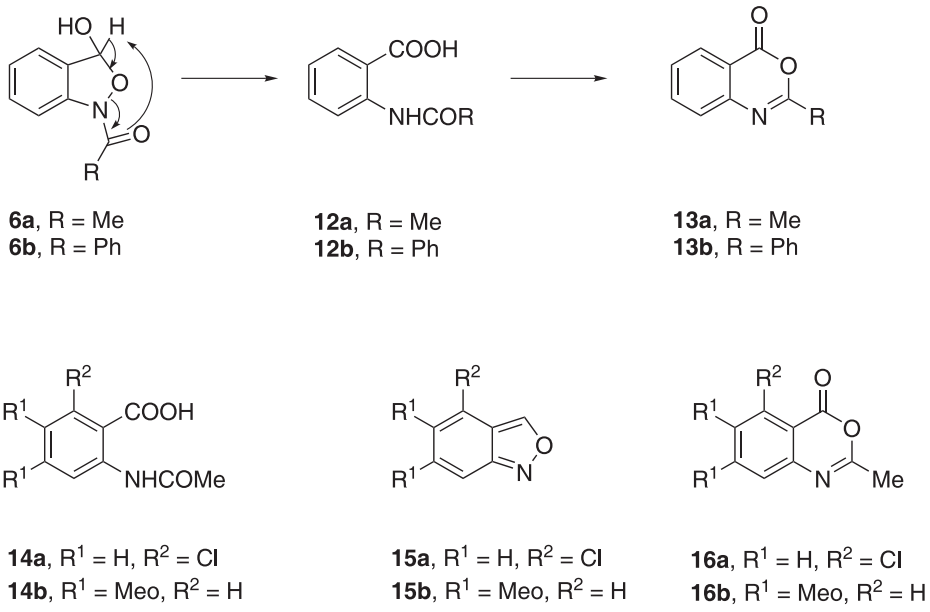
Whereas **9a** also exists predominantly in the cyclic form (> 95 %) in solution and in the solid state, the ^{1}H NMR (DMSO) spectrum of the dimethoxy compound **9b** shows that it is a 2:3 mixture of the cyclic and open chain forms **9b** and **10,** respectively. Both forms are also clearly recognizable in the ^{13}C NMR spectrum (see experimental section). In CD_3CN solution, equal amounts of the two forms are present at room temperature, but the aldehyde form is favored over the cyclic form (3:2) at 330 ºK. As judged by the absence of an aldehyde carbonyl stretching band in the IR spectrum, this substance exists totally as the cyclic tautomer in the solid state.

The generation of the putative hydroxylamino compound **4a** was investigated next. This substance is reported to be a stable crystalline solid, mp 87 ºC, which was isolated by column chromatography on silica gel, and was converted into the amine **4c** on catalytic reduction. All of the reported spectroscopic data are consistent with that expected for **4a,** except that the aldehyde CH is found at δ 9.09 in the NMR spectrum. This is > 1 δ upfield of the chemical shift for the vast majority of aldehydes (δ 10-10.5). Reduction of the nitro compound **4b** with the zinc /ammonium chloride system gave a solution which by TLC, contained a little of the amino compound **4c** and a major amount of a more polar material. Separation of this mixture by column chromatography on silica gel gave the aminoaldehyde **4c** (~ 20 %) and a stable crystalline compound, mp 91.5-93 º C (*ca* 70 %). Both the crystalline material, and the ethyl acetate solution of the crude reduction mixture were completely inert to acylation with acetyl chloride under conditions which were successful for the synthesis of **6a-c**, **9a**, and **9b**. The ^{1}H NMR spectrum of the pure material precisely matched that reported by Blanco, et. al. [5] except for a broad absorption at δ 5.40, which was not found in the material described in this work. Furthermore, the ^{13}C NMR spectrum also matched well with that described, but the reported absorption for the aldehyde carbon (δ 191.73) was not observed in our material. An absorption at δ 152.58, not reported by Blanco, *et. al.* was, however, present in the material described herein. All of the spectroscopic and chemical properties of this crystalline compound are consistent with the anthranil structure **11**. The δ 9.09 absorption is assignable to H-3, and is found in all of the 3-unsubstituted anthranils (δ 8.8-9.2) that we and others [8] have studied. In addition, the δ 152.58 absorption is due to C-3 and is also present in the ^{13}C spectra of the 3-unsubstituted anthranil derivaties (δ 152.0-155.2) that we and Kim, *et. al.* [8] have examined. In addition, the 1650 cm^{-1} IR band which Blanco, *et. al.* [5] assigned to the aldehyde carbonyl stretching absorption of **4a**, is present in 3-unsubstituted anthranils (1655-1635 cm^{-1}). Finally, Fernández, *et. al.* [9] reported that the anthranil **11**, was obtained as an intermediate on catalytic reduction of **4b** to the amine **4c**. The data (IR, ^{1}H NMR) which they list, match ours closely, although their melting point (62-64 ºC) differs considerably from what we and Blanco, *et. al.* [5] observed.

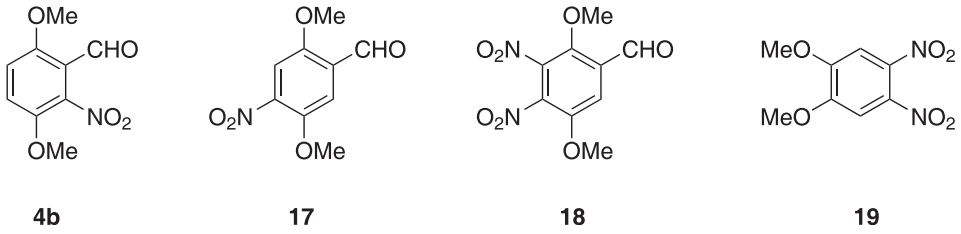
During the course of determining the melting points of the *N*-acylated *o*-hydroxylaminobenz-aldehydes, it was observed that these substances melted with decomposition, and in all cases the so-produced melt resolidified giving a material with a very different melting point. A preparative scale thermal decomposition of the *N*-benzoyl compound **6b** at its melting point (132 ºC) gave a less polar, crystalline solid, mp 121-122 ºC (68 % yield) which clearly was not anthranil. The IR spectrum possesed an intense band at 1765 cm^{-1}, and the mass spectrum showed that the new compound differed from **6b** by 18 mass units. These data were uniquely consistent with those expected [10] for the benzoxazinone **13b** (Scheme 3), which was confirmed by direct comparison with an authentic specimen. The formation of **13b** from **6b** is suggested to take place by an internal redox process to give *N*-benzoylanthranilic acid **12b** as an intermediate, which then undergoes intramolecular dehydration (Scheme 3). The thermal dehydration of *N*-benzoylantharanilic acid **12b** to **13b** is a well recognized phenomenon [11]. The above redox dehydration sequence on **6b** could also be effected, although much more slowly, in boiling *m*-xylene, in which case both the benzoxazinone **13b** and a small amount of the anthranilic acid **12b** (8 %) were obtained. The *N*-acetyl compound **6a** similarly underwent the above sequence of reactions in *m*-xylene to give N-acetylanthranilic acid **12a** and the expected benzoxazinone **13a** in *ca* 21 % and 65 % yields, respectively. Furthermore, **12a** was converted into **13a** under these conditions. The thermolysis of **9a** and **9b** was examined only in a cursory manner. When heated neat at its melting point, the chloro compound **9a** was converted into the anthranilic acid derivative **14a** (38 %), and a small amount of the anthranil **15a**, but none of the benzoxazinone **16a** was formed. Thermolysis of **9b** in the same way gave the anthranilic acid **14b** (22 %), the benzoxazinone **16b** (45 %), but none of the anthranil **15b**.

The first, and to date only, reported example of the above interesting internal redox process was described by Bamberger [2] who obtained *N*-acetylanthranilic acid **12a** in 55 % yield upon brief heating of **6a** slightly above its melting point. He did not, however, observe the intramolecular dehydration of **12a** to the benzoxazinone **13a**.

A few comments regarding the synthesis of 2-nitro-3,6-dimethoxybenzaldehyde (**4b**), the precursor of anthranil **11**, are in order. This compound was first prepared by Rubenstein [12], by the nitration of 2,5-dimethoxybenzaldehyde (**4d**) with concentrated nitric acid (0 ºC - room temp.). This nitration (room temp.) was repeated by Blanco, *et. al.* [13, 14)], was said to be difficult to reproduce, not easily scaled up, and was reported to give a 2.5 : 1 mixture of **4b** and the isomeric nitro compound **17** (Scheme 4, Table 1, Entry 1). They also describe conditions for this nitration in acetic acid-ether solution, which are said to be free of the above problems, and provided a 2:1 mixture of **4b** and **17** (Entry 2). Thummel, et. al. [15] disclosed conditions for the nitration of **4d** using nitric acid supported on silica gel in dichloromethane solution at room temperature, under ultrasonic irradiation, which generated a mixture in which **4b** was favored over **17** by a factor of 4.3 (> 95 % yield; Entry 3). In our hands, none of these procedures gave precisely the results reported. The nitration in acetic acid-ether solution had a long induction period (24 h),



Scheme 3



Scheme 4

Table 1. Nitration of 2,5-Dimethoxybenzaldehyde (**4d**).

Entry	Nitration method	Temp.	% **4b**	% **17**	Reference
1	conc. HNO_3	r.t.	64	26	13
2	HNO_3 - Ether - HOAc	r.t.	60	29	13
3	HNO_3 on SiO_2 in CH_2Cl_2[a]	r.t.	78	18	15
4	HNO_3 - Ether - HOAc	r.t.	40	26	This work
5	Add **4d** in CH_2Cl_2 to HNO_3 on SiO_2	r.t.	37	25	This work
6	Add HNO_3 on SiO_2 to **4d** in CH_2Cl_2	r.t.	49	27	This work
7	conc. HNO_3	3-8 ºC	67	11	This work

[a]Sonication.

then required a further 24 h for completion, and generated a 1.5 :1 mixture of **4b** and **17** (Entry 4). When nitric acid on silica gel was used, both the reaction rate and the product distribution were dependant on the addition order. Addition of 2,5-dimethoxybenzaldehyde in a small volume of dichloromethane (4 mL /g) to the supported nitrating reagent (20 g/g **4d**), and subsequent mechanical agitation, resulted in completion of the reaction in < 10 min, and favored **4b** over **17** by a factor of 1.5 (Entry 5). Addition of the supported nitrating agent to a dichloromethane solution of **4d** (40 mL/g), resulted in a slow reaction (8 h), which was not accelerated by ultra sound, and gave a 1.8:1 mixture of **4b** and **17** (Entry 6). Nitration in concentrated nitric acid at room temperature, as described by Blanco, *et. al*. [13] was complicated by the formation of polynitration products such as **18**. In contrast, when this nitration was effected at ice-bath temperature, the reaction was essentially complete in 10 min, gave a 6:1 mixture of **4b** and **17** from which **4b** could be isolated in nearly 70 % yield (Entry 7). This is an easily reproducible, and rapid method for the generation of substantial quantities of **4b**.

Experimental

For general procedures, see reference 16. The ^{1}H NMR spectra were measured at 300 MHz. Column chromatographic separations were effected using 230-400 mesh silica gel. The columns were packed dry, successively layered with the crude reaction mixture (absorbed onto silica gel), and a small amount of sand, and then eluted with the appropriate solvent system. The mixtures absorbed on silica gel were prepared by dissolving the reaction mixture in dichloromethane, adding the solution to silica gel, and then removing the solvent *in vacuo*. Commercial 2-nitro-4,5-dimethoxybenzaldehyde (**8b**) contains 10-20% of 1,2-dinitro-4,5-dimethoxybenzene (**19**) which cannot be readily removed by crystallization or by column chromatograpy. Pure **8b**, is readily obtained, however, by vigorously stirring a dichloromethane solution of the mixture with aqueous sodium bisulfite (2 equiv) for 3-4 h. The pure aldehyde is recovered from the aqueous phase, by the addition of excess sodium carbonate, extraction with dichloromethane and crystallization of the crude product from ethanol. About 85 % of the pure aldehyde is recovered in this way.

2-Nitro-3,6-dimethoxybenzaldehyde (4b). Finely ground 2,5-dimethoxybenzaldehyde (**4d**, 1.0 g, 6.02 mmol) was added in one portion to concentrated nitric acid (12 mL) cooled in an ice bath. The reaction temperature rose from 3 ºC to 8 ºC (Larger scale reactions required portionwise addition to prevent the temperature from exceeding 10 ºC.), the aldehyde dissolved, and almost immediately a yellow solid began to separate from solution. The starting material was no longer detectable by TLC after 10 min, and the mixture was poured onto crushed ice. The mixture was extracted with dicloromethane, the extract was washed to neutrality with water, dried, and the solvent was removed in vacuo. The residual yellow solid (1.18 g) was absorbed onto silica gel (6 g) and purified by column (4.2 × 18 cm) chromatography on silica gel (120 g) using ethyl acetate-hexane (25:75; 25 mL fractions) as the eluant. Fractions 1 and 2 contained the 4-nitro compound **17** (0.235 g), and fractions 9-26 contained **4b** (0.857 g, 67.4 %), mp 165-167 ºC, reptd. [15] mp 163-165 ºC. Crystallization of the crude 4-nitro compound from ethanol gave pure material (0.145 g, 11.4 %) mp 170-171 ºC, reptd. [15] mp 157-161 ºC.

Phenylhydroxylamine (**7b**). A mixture of nitrobenzene (2.46 g, 20 mmol), zinc powder (4.82 g, 75.3 mmol), ammonium chloride (6.72 g, 125.6 mmol), water (120 mL), and ethyl acetate (200 mL) was vigorously stirred at room temperature for 5 h. The organic phase was separated, the aqueous phase was saturated with NaCl, and extracted with ethyl acetate. The organic phases were combined, washed with saturated NaCl solution, and dried over Na_2SO_4. The crude product was slurried with hexane, pulverized with a glass rod, and cooled in the refrigerator. Phenylhydroxylamine (1.71 g, 78.3 %) was obtained as a white, needle shaped, crystalline solid, mp 81-83 ºC, reptd. [17] mp 80-81 ºC].

Synthesis of o-hydroxylaminobenzaldehyde (1a). A mixture of *o*-nitrobenzaldehyde (**1b**) (1.51 g, 10 mmol), zinc powder (2.46 g. 37.6 mmol), ammonium chloride (3.36 g, 62.8 mmol), water (60 mL), and ethyl acetate (100 mL), was stirred vigorously at room temperature for 1.5 h. The organic phase was separated, combined with an ethyl acetate extract of the aqueous phase, the extract was washed with saturated NaCl solution, and dried. Ethyl acetate solutions of the hydroxyalmino compound can be kept at 5 ºC for several days without significant decomposition. An aliquot of this solution was rapidly evaporated *in vacuo* below room temperature and the NMR spectral meaurements were made immediately. Integration of the appropriate resonances showed that the mixture consisted of **1a** (65.5 %), *o*-nitrobenzaldehyde (**1b**, 7 %), 2-aminobenzaldehyde (**1c**, 5.5 %), and anthranil (**2**, 21.5 %). 2-Hydroxylaminobenzaldehyde had the following NMR spectral data. ^{1}H NMR ($CDCl_3$) δ 6.98 (td, 1H, J = 7.4, 1.1 Hz), 7.35 (d, 1H, J = 7.4 Hz), 7.53 (td, 1H), 7.60 (dd, 1H, J = 7.7, 1.5 Hz), 9.74 (bs, 1H, exchanged with D_2O), 9.83 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 113.54, 119.39, 124.81, 135.80, 136.13, 152.65, 194.25.

2-Hydroxylamino-6-chlorobenzaldehyde (**8c**) **and 2-hydroxylamino-4,5-dimethoxybenz-aldehyde** (**8d**). Ethyl acetate solutions of these compounds were prepared from the corresponding nitro compounds **8a** and **8b** in exactly the same manner as described for the synthesis of **1a,** except that the reduction required 3-4 h to reach completion. These solutions were used immediately to prepare the *N*-acetyl compounds.

N-Acylation of the *o*-hydroxylaminobenzaldehydes. Synthesis of the *N*-acetyl compound 6a. *o*-Nitrobenzaldehyde was reduced on a 20 mmol scale as

described above. The ethyl acetate solution was cooled in an ice-salt bath and a solution of $NaHCO_3$ (18 mmol) in water (20 mL) was added with vigorous stirring. When the aqueous phase had frozen, a solution of acetyl chloride (1.0 mL, 1.10 g,14.06 mmol) in ethyl acetate (25 mL) was added over a 5 min period. The mixture was then stirred at ice-bath temperature for 1 h and at room temperature for 1 h. The organic phase was separated, and combined with an ethyl acetate extract of the aqueous phase. The ethyl acetate solution was washed with saturated NaCl solution, dried, and the solvent was removed *in vacuo* to give a semi-solid residue (2.71 g). This was dissolved in hot ethyl acetate (5 mL), diluted with hexane (5 mL) and seeded. A solid (0.957 g, mp 120-122 ºC, dec), which gave a strong positive test with 1 % methanolic ferric chloride [18], was obtained. The mother liquor was evaporated and the residue (1.75 g) was absorbed onto silica gel (9 g), loaded onto a dry packed column (6 × 24.5 cm) of silica gel (350 g), and eluted with ethyl acetate-hexane (30:70; 50 mL fractions). Fractions 6-8 contained anthranil (0.515 g), and the desired product (0.236 g) was found in fractions 40-65. Crystallization of this material from 1:1 ethyl acetate-hexane gave a further 0.167 g of the product, mp 122-123 ºC, dec [yield, 1.124 g, 52.3 % (based on an assumed 60 % yield (12 mmol) of the hydroxylamino compound **1a**] . A specimen of this material on recrystallization and drying *in vacuo* at 50 ºC for 16 h had mp 122.5-124 º C; IR (KBr) 3312, 1641 cm^{-1}; ^1H NMR (DMSO, d_6) δ 2.23 (s, 3H), 6.65(d, 1H, J = 8.1 Hz, singlet after D_2O exchange), 7.49(td, 1H, J = 7.2, 0.95 Hz), 7.44(m, 2H), 7.94(d, 1H, J = 7.7 Hz), 7.81(d, 1H, J = 8.1 Hz, exchanged with D_2O); ^{13}C NMR δ 22.01, 99.24, 113.61, 124.02, 124.92, 129.00, 130.15, 136.74, 166.98. Anal. calcd. for $C_9H_9NO_3$: C 60.33, H 5.06, N 7.82: found: C 60.60, H 5.01, N 7.95.

Synthesis of the N-benzoyl compound 6b. This compound was prepared from a stock solution of **1a** (169 mL, estimated to contain 5.5 mmol) in ethyl acetate and benzoyl chloride (0.50 g, 6.05 mmol) as described above for **6a**. The crude partially solid product (1.19 g) was taken up in hot ethyl acetate (4 mL), diluted with hexane (1 mL) and seeded. The solid (0.653 g) which separated was not pure and therefore was absorbed onto silica gel (3.5 g), loaded onto a dry packed column (6 × 10 cm) of silica gel (131 g), and eluted with ethyl acetate-hexane (25:75, 50 mL fractions). The desired product (0.492 g, mp 131.5-132.5 ºC) was contained in fractions 12-21. The mother liquor from the above crude crystalline material was evaporated, and the residue (0.56 g) was absorbed onto silica gel (3 g), placed on top of a dry packed column (4.2 x 17 cm) of silica gel (111 g), and the product (0.214 g, mp 130.5-132.5 ºC) was found in fractions 10-15. The yield of pure material was (0.706 g, 53.2%); it gave a deep purple color with methanolic ferric chloride solution. A portion was taken up in hot ethyl acetate, diluted with an equal volume of hexane, and seeded to give analytically pure material, mp 132-134 ºC.; IR (KBr) 3423, 3224, 1616 cm^{-1} ; ^1H NMR (DMSO d_6) δ 6.69 (d, 1 H, J = 7.9 Hz, singlet after D_2O exchange), 7.29 (dt, 1H, J = 7.5, 0.91 Hz), 7.47-7.62 (m, 5H), 7.86-7.89 (m, 3H), 7.88 (d, 1H, J = 7.9 Hz, exchanged with D_2O); ^{13}C NMR δ 99.62, 114.61, 124.05, 125.55, 128.44, 129.28, 129.31, 130.20, 131.90, 133.63, 137.24, 164.57. Anal. calcd. for $C_{14}H_{11}NO_3$: C 69.70, H 4.60, N 5.81; found: C 69.81, H 4.60, N 5.86.

Synthesis of the *N*-benzyloxycarbonyl compound 6c. The crude product (0.77 g) obtained from a 5 mmol scale reduction of **1b**, was absorbed onto silica gel (4 g) and subjected to chromatographic purification on a column (6 × 16.5 cm) of silica gel (232 g) using ethyl acetate-hexane (25:75; 50 mL fractions) as the eluting solvent. The crystalline product (0.174 g, 21.4 % yield based on an assumed 60 % yield in the reduction) was twice crystallized from toluene to give analytically pure material, mp 141-141.5 ºC; IR (KBr) 3418, 1682 cm^{-1}; ^1H NMR (DMSO, d_6) δ 5.31 (s, 2H), 6.60 (d, 1H, J = 7.6 Hz, singlet after D_2O exchange), 7.17-7.22 (m, 2H), 7.36-7.48 (m, 7H), 7.73 (d, 1H, J = 7.6 Hz, exchanged with D_2O); ^{13}C NMR δ 67.81, 99.09, 113.08, 124.04, 124.65, 128.59, 128.77, 128.91, 130.16, 136.07, 137.82, 151.93. Anal. calcd. for $C_{15}H_{13}NO_4$: 0.1 C_7H_8: C 67.23, H 4.96, N 4.99; found: C 67.19, H 4.85, N 5.27. The presence of *ca* 0.07 mol toluene was confirmed by a singlet at δ 2.30 in the NMR spectrum.

Synthesis of the *N*-acetyl chloro compound 9a. The crude, solid acetylation product (1.60 g) obtained from a 10 mmol scale reduction of **8a**, was slurried with ethyl acetate and the insoluble material (0.433 g, mp 135-137 ºC) was collected by filtration and dried in vacuo. The mother liquor was evaporated *in vacuo*, and slurried with dichloromethane to give additional product (0.082 g, mp 139-139.5 ºC; total yield, 0.485 g; 37.8 % based on an assumed 60 % yield of **8c**). This compound cannot be purified by column chromatography on silica gel; it is converted into the corresponding anthranil **15a**. Crystallization from ethyl acetate gave analytically pure material, mp 143-143.5 ºC; IR (KBr) 3234, 1640 cm^{-1}; ^1H NMR (DMSO, d_6) δ 2.25 (s, 3H), 6.64 (d, 1H, J = 8.1 Hz, singlet after D_2O exchange), 7.26 (dd, 1H, J = 8.0, 0.91 Hz), 7.47 (t, 1H), 7.63 (d, 1H, J = 7.85 Hz), 8.02 (d, 1H, J = 8.1 Hz, exchanged with D_2O); ^{13}C NMR δ 72.01, 98.31, 112.51, 124.97, 126.68, 128.68, 132.25, 138.32, 167.54. Anal. calcd. for $C_9H_8ClNO_3$: C 50.60, H 3.77 N 6.56; found: C 50.81, H 3.77, N 6.65.

Synthesis of the *N*-acetyl dimethoxy compound 9b. The crude, solid acetylation product (1.97 g) from a 10 mmol scale reduction of **8b** was slurried with ethyl acetate and the insoluble material was collected by filtration, dried, and then crystallized from toluene. A solid (0.576 g, 40.1 % yield based on an assumed 60 % yield of **8d**) which gave a deep purple color with methanolic ferric chloride, and which had mp 122-122.5 ºC was obtained, IR (KBr) 3400, 3206, 1632 cm^{-1}; ^1H NMR (DMSO, d_6) δ 2.20 (s, 1.6H), 2.22 (bs, 1.2H), 3.76 (s, 1.2H), 3.79 (s, 1.2H), 3.84 (s, 1.8H), 3.88 (s, 1.8H), 6.57 (d, 0.4H, J = 8.05 Hz, singlet after D_2O exchange), 7.04 (s, 0.4H), 7.07 (s,

0.6 H), 7.25 (s, 0.6 H), 7.32 (s, 0.4H), 7.69 (d, 0.4H, J = 8.05 Hz, exchanged with D_2O), 9.82 (s, 0.6H), 10.83 (bs, 0.6H, exchanged with D_2O); ^{13}C NMR δ 21.56, 21.85, 56.09, 56.20, 56.46, 98.25, 99.69, 107.16, 107.85, 109.15, 119.79, 123.89, 130.82, 138.81, 146.77, 148.62, 150.39, 154.41, 166.26, 188.80; MS [EI] m/z (%) 239 [M^+] (57), 197 [M - MeCO + H] (100), 180 (43), 179 (43), 164 (79), 149 (42), 136 (52); HR-ES-CH_3CN-MS m/z calcd for $C_{11}H_{13}NO_5$ + CH_3CN + Na: 303.0957: found: 303.0971.

Synthesis of the anthranil 11. A mixture of the nitro compound **4b** (1.056 g, 5.0 mmol), ammonium chloride (2.52 g, 47.1 mmol), zinc powder (1.86 g, 28.4 mmol), ethyl acetate (75 mL), and water (30 mL) was stirred vigorously for 3 h, and then worked up as described above. If the usual quantities of zinc powder and ammonium chloride were used, the reduction was inordinately slow. The ethyl acetate solution was evaporated *in vacuo* to give a solid which was absorbed onto silica gel (4 g) and then subjected to column (6 × 18.5 cm) chromatographic purification on silica gel (259 g) using ethyl acetate hexane (25:75; 50 mL fractions) as the eluant. Fractions 11-17 contained the crystalline amino compound **4c** (0.208 g, 23.0 %, mp 66-68 ºC, reptd. [15] mp 67-68 ºC), and fractions 20-30 contained the anthranil **11** (0.603 g, 67.3 %, mp 91.5-93 ºC, reptd (5) mp 87 º C). For a discussion of the spectroscopic properties of this compound see the results and discussion section.

Solid phase thermolysis of the *N*-acylated *o*-hydroxylaminobenzaldehydes. The solid *N*-acyl compound, contained in a round bottomed flask under an argon atomosphere, was placed in an oil bath at a temperature which was ca 5 ºC below its decomposition point. When the decomposition temperature was reached vigorous bubbling occurred, and when this subsided the resulting melt sometimes crystallized. The vessel was removed from the bath (total reaction time *ca* 10 min) and the crude product was then worked up as described below for the specific thermolyses.

2-Phenyl-4H-3,1-benzoxazin-4-one (13b). The crude product (0.179 g) from a 0.804 mmol scale reaction of **6b** was absorbed onto silica gel (1 g) and purified by column (3.4 x 11 cm) chromatography on silica gel (54 g) using ethyl acetate-hexane (15:85; 20 mL fractions) as the eluant. The benzoxazinone **13b** (0.122 g, 68.0 %) was found in fractions 3-9. Recrystallization from cyclohexane gave 0.110 g of pure material, mp 120-122 ºC, undepressed on admixture with an authentic specimen.

***N*-Acetyl-6-chloroanthranilic acid (14a) and anthranil (15a)**. The crude solid from a 1.21 mmol scale thermolysis of **9a** was partitioned between ethyl acetate and 10 wt. % sodium carbonate solution. The organic phase was washed with saturated NaCl solution, dried, and evaporated in vacuo to give a solid (.093 g) which by TLC (25:75 EtOAc-hexane) showed the presence of the anthranil **15a** and several other materials, none of which corresponded to the benzoxazinone. The carbonate phase was brought to pH 1 with 3M HCl, and extracted with ethyl acetate. The extract was washed successively with water and saturated NaCl solution, dried and evaporated *in vacuo*. Toluene was added to the solid residue to remove residual acetic acid, and the mixture was evaporated to dryness *in vacuo* to give **14a** (0.098 g, 37.8 %), mp 204-207 ºC, reptd (19) mp 212-215 ºC. ^1H NMR (DMSO, d_6) δ 2.01 (s, 3H), 7.32 (dd, 1H, J = 7.0, 1.1 Hz), 7.41 (t, 1H), 7.47 (dd, 1H, J = 8.0, 1.1 Hz), 9.67 (s, 1H, exchanged with D_2O),13.55 (bs, 1H, exchanged with D_2O); ^{13}C NMR δ 23.57, 124.77, 126.27,130.21, 130.76, 136.68, 166.42, 169.14.

***N*-Acetyl-4,5-dimethoxyanthranilic acid (14b) and 2-methyl-4H-6,7-dimethoxy-3,1-benzoxazin-4-one (16b)**. The sodium carbonate soluble material from a 1 mmol scale thermolysis of **9b** gave the carboxylic acid **14b** as a solid (0.053 g, 22.2 %), mp 221-224 ºC, reptd. [20] mp 223.5-224.5 ºC. ^1H NMR (DMSO, d_6) δ 2.12 (s, 3H), 3.76 (s, 3H), 3.80 (s, 3H), 7.42 (s, 1H), 8.26 (s, 1H), 11.14 (s, 1H, exchanged with D_2O), 13.32 (bs, 1H, exchanged with D_2O); ^{13}C NMR δ 25.45, 55.88, 55.94, 103.47, 113.14, 137.24, 143.74, 153.49, 168.61, 169.59. The neutral phase on evaporation gave a solid which was crystallized from ethyl acetate to give **16b** as an orange colored solid (0.101 g, 45.7 %) mp 182-183 ºC, reptd. [20] mp 185-186.5 ºC. IR ($CHCl_3$) 1738, 1644, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.45 (s, 3H), 3.97 (s, 3H), 3.99 (s, 3H), 6.96 (s, 1H), 7.49 (s, 1H); ^{13}C NMR δ 21.65, 56.79, 56.84, 107.81, 109.49, 149.89, 156.81, 159.93, 160.04.

Solution phase thermolysis of the *N*-acylated *o*-hydroxylaminobenzaldehydes. A solution of the N-acyl compound in *m*-xylene (10 mL / 0.1 g substrate) was heated at reflux temperature in an argon atmosphere until TLC showed that the starting material was no longer present. The solvent was removed *in vacuo* and the residue was then worked up as described below for the particular substrate.

***N*-Acetylanthranilic acid (12a) and 2-methyl-4H-3,1-benzoxazin-4-one (13a)**. After **6a** was heated 6 h at reflux temperature the crude product was partitioned between ethyl acetate and 10 wt. % sodium carbonate solution. The base soluble and neutral phases gave **12a** (21.3 %) and **13a** (64.9 %) respectively, both of which were spectroscopically identical to commercial samples. A sample of **12a** on heating at reflux temperature for 7 h gave **13a** in ca 37 % yield, and a considerable amount of **12a** was recovered (63 %).

***N*-Benzoylanthranilic acid (12b) and 2-phenyl-4H-3,1-benzoxazin-4-one (13b)**. The crude solid (0.146 g) from a 0.60 mmol scale thermolysis of **6b** was absorbed onto silica gel (0.75 g) and purified by column (2.2 × 16.5 cm) chromatography on silica gel (29.3 g) using ethyl acetate-hexane (20:80; 15 mL fractions) as the eluant The product was found in fractions 3 and 4 and was crystallized from cyclohexane to give **13b** (0.081 g, 60.5 %), mp. 121-123 ºC. The crude product

from another reaction was partitioned between ethyl acetate and 10 wt. % sodium carbonate solution. *N*-Benzoylanthranilic acid (**12b**, 8.3 %), isolated from the basic phase, was spectroscopically identical to an authentic specimen.

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