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Reexamination of the Thermolytic Rearrangement of 4-Halophenyl Azides to 2-Aminophenols and other Products

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Summary. The halogenation of derivatives of 2-aminophenol with N-chloro- and N-bromosuccinimides at ambient temperatures in acetic acid was studied. With the necessary compounds available, a reexamination of the thermolytic rearrangement of 2-halophenyl azides to 2-aminophenols and other products was undertaken. It is certain that the rearrangement of 4-halophenyl azides to 2-aminophenols occurs but the products identified in this study differ significantly from those reported previously by Suschitzky et al. (1963, 1966).

Keywords. Acetylated-2-amino-5-halophenols; 2-Acetamido-5-haloanisoles; 6-Halo-2-methylbenzoxazoles; 6-Halobenzoxazolones; 6-Halotriacetylaminophenols; ^{1}H-NMR spectra; Fungicidal activity.

Neuuntersuchung der thermolytischen Umlagerung von 4-Halogenphenylaziden zu 2-Aminophenolen und anderen Produkten

Zusammenfassung. Es wurde die Halogenierung von 2-Aminophenol-Derivaten mit N-Chlor- und N-Bromsuccinimid bei Raumtemperatur in Essigsäure untersucht. Mit den zur Verfügung stehenden Verbindungen konnte eine Neuuntersuchung der thermolytischen Umlagerung von 4-Halogenphenylaziden zu 2-Aminophenolen und anderen Produkten unternommen werden. Diese Umlagerung findet sicherlich statt, allerdings differieren die dabei beobachteten Produkte signifikant von denen, die Suschitzky et al. 1963 und 1966 beschrieben.

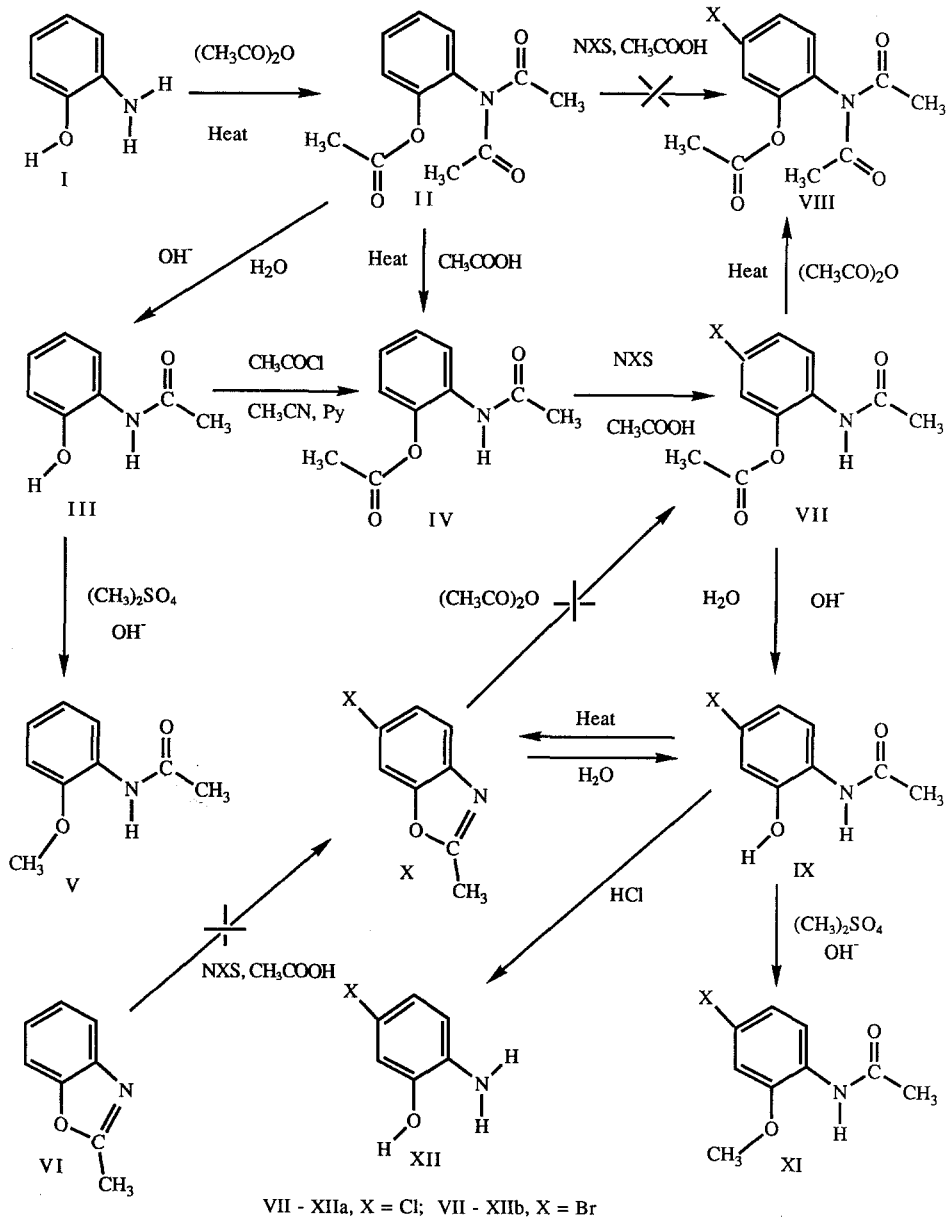
Introduction

In a recent report on monohalogenated 8-quinolinols we included the preparation and characterization of 2-acetamido-5-bromophenyl acetate [1]. The melting point (163–4 °C) of this product was distinctly different from that reported previously (128 °C [2]; 125 °C [3]). These latter preparations were characterized by melting points, carbon and hydrogen analyses and a non-depressed melting point of a mixture of the two products. No ^{1}H-NMR spectrum or bromine analysis was reported. These would have offered more precise evidence to prove the structures reported. We therefore decided to undertake an investigation of the halogenation of derivatives of 2-aminophenol with N-chloro- (*NCS*) and N-bromosuccinimides (*NBS*) to try to clarify this apparent discrepancy.

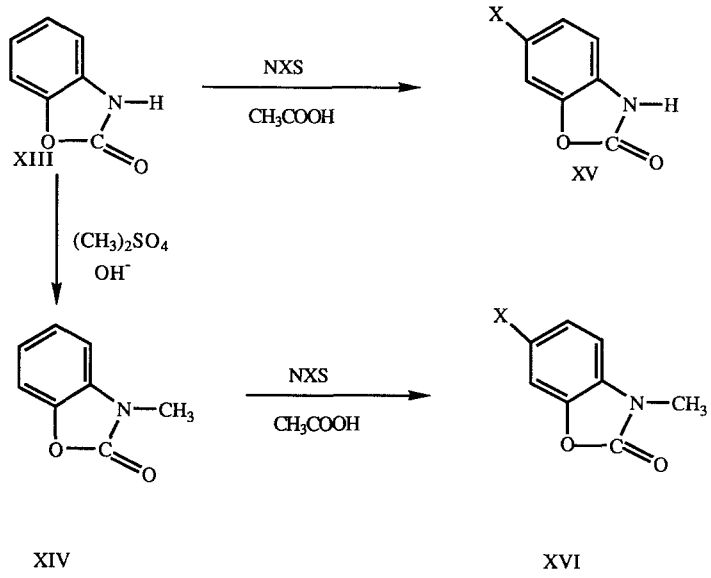
Results and Discussion

The sequences of reactions in this study are summarized in Schemes 1 and 2, and in all cases, the products were made by unambiguous methods and characterized by ^{1}H-NMR to establish structures of the compounds.

2-Aminophenol (**I**) was converted to N,N,O-triacetyl-2-aminophenol (**II**) by heating with acetic anhydride. On saponification of **II** with aqueous alkali 2-acetamidophenol (**III**) was obtained which was esterified with acetyl chloride in acetonitrile in the presence of pyridine to yield pure 2-acetamidophenyl acetate (**IV**). Alternatively, **IV** could be obtained, equally pure, by heating **II** in acetic acid. The



Scheme 1



Scheme 2

generally employed method for preparing **IV** [4] yielded mixtures of **II** and **IV**. Methylation of **III** with methyl sulfate afforded 2-acetamidoanisole (**V**).

Attempts to halogenate **II** with either *NCS* or *NBS* in acetic acid after stirring for two weeks at ambient temperatures failed. On reacting **IV** with *NCS* and *NBS* respectively, in acetic acid, 2-acetamido-5-chlorophenyl acetate (**VIIa**) and the corresponding bromo analogue (**VIIb**) were obtained. Both N,N,O-triacetyl-5-chloro-2-aminophenol (**VIIIa**) and the corresponding bromo compound (**VIIIb**) were obtained from **VIIa** and **VIIb** by heating with acetic anhydride. On saponification of **VIIa** and **VIIb** with aqueous alkali 2-acetamido-5-chlorophenol (**IXa**) and 2-acetamido-5-bromophenol (**IXb**) were obtained. These were subsequently methylated with methyl sulfate to yield 2-acetamido-5-chloroanisole (**XIa**) and the corresponding bromo analogue (**XIb**). Hydrolysis of **IXa** and **IXb** by means of hydrochloric acid afforded 5-chloro- (**XIIa**) and 5-bromo-2-aminophenol (**XIIb**). When halogenation of 2-methylbenzoxazole (**VI**) with *NCS* or *NBS* in acetic acid was attempted, no halo product was obtained, but on pyrolysis of **IXa** and **IXb** the respective 6-chloro-2-methyl- (**Xa**) and 6-bromo-2-methylbenzoxazoles (**Xb**) were formed. Compounds **Xa** and **Xb** were unstable in warm water with the oxazole rings opening to form **IXa** and **IXb** respectively.

It appeared that nonhalogenation of **II** and **VI** could have been due to the absence of a hydrogen atom on the nitrogen. To test this hypothesis benzoxazolinone (**XIII**) and N-methylbenzoxazolinone (**XIV**), obtained by methylation of **XIII**, were subjected to halogenation with *NCS* and *NBS* in acetic acid. The respective 6-chloro- (**XVa**) and 6-bromobenzoxazolinones (**XVb**) and 6-chloro- (**XVIa**) and 6-bromo-N-methylbenzoxazolinones (**XVIb**) were all formed in good yield. It remains unclear as to why **II** and **VI** could not be halogenated whereas **XIII** and **XIV** were easily halogenated by this procedure.

With most of the expected compounds available, and understanding their reactivities, we undertook a reexamination of the experiments of Suschitzky et al. [2, 3] along with some variations of the methods employed. In the study of the thermolysis of 4-substituted phenyl azides in acetic anhydride it was claimed that only substituted 2-aminophenols, amines and azo compounds were formed [2]. It should be noted that it was previously reported that when 2-aminophenol was heated in acetic anhydride 2-methylbenzoxazole was formed in good yield [7]. When a mixture of acetic and polyphosphoric acids was employed for the thermolytic reaction of the 4-halophenyl azides, only 2-acetamido-5-halophenyl acetates were claimed to be the products [3]. In view of this we also prepared 4-chloroacetanilide [8], 4-bromoacetanilide [9], N,N-diacetyl-4-chloroaniline [10], N,N-diacetyl-4-bromoaniline [12] 4,4′-dichloroazobenzene [11] and 4,4′-dibromoazobenzene [11].

Both 4-chloro- and 4-bromophenyl azides [12] were heated under reflux in acetic anhydride for 15 h [2] and in stainless steel pressure vessels at 140 °C for the same length of time. Similar treatments were carried out in glacial acetic acid. 4-Bromophenyl azide was also thermolyzed in a mixture of acetic acid and polyphosphoric acid at 140 °C for 2 h [3]. Aliquots of the reaction mixtures in acetic anhydride and acetic acid, diluted with acetonitrile, were subjected to gas chromatographic analysis. The reaction mixture formed in polyphosphoric acid was cooled, diluted with ice water and extracted with chloroform. An aliquot of the chloroform extract was freed of this solvent under a stream of nitrogen, dissolved in hot acetonitrile and assayed in the gas chromatograph. After observing the results of this chromatogram in which a large percentage of 2-acetamido-5-bromophenol (**IXb**) was detected, and also recognizing that upon gas chromatographing this compound a significant amount of 6-bromo-2-methylbenzoxazole (**Xb**) was a co-product due to pyrolysis of **IXb**, the residue of the chloroform extract was slurried with cold acetonitrile. The insoluble material was removed by filtration and the filtrate was gas chromatographed and found to be free of **IXb**. The crystalline product was nearly pure **IXb**. The results of the various thermolytic conditions are summarized in Tables 1 and 2.

Thermolysis of both of the 4-halophenyl azides in acetic acid yielded similar products (Table 1). The reaction appears to be temperature dependent. At 140 °C 2-methyl-6-halobenzoxazoles (**Xa, Xb**) were obtained in 100% and 98% yield respectively. At reflux temperature **Xa** and **Xb** were obtained in 50% and 40% yield each and the remainder of the mixtures were starting materials. When thermolysis was carried out in acetic anhydride, the reflux temperatures and that in the pressure vessels were nearly the same. The products of both treatments (**Xa, Xb**, N,N-diacetyl-4-chloro- and 4-bromoanilines, **VIIIa, VIIIb**) were the same, and the yields of products derived from 4-bromophenyl azide resulting from the mixtures were also nearly the same. The yields of products derived from 4-chlorophenyl azide were significantly different in that N,N-diacetyl-4-chloroaniline in the pressure vessel was formed in twice the yield of that obtained as a result of heating under reflux, and **VIIIa** was one third in the pressure vessel compared to that under reflux. It maybe that escape of nitrogen resulting from the thermolytic reaction favors the formation of **VIIIa** over the N,N-diacetyl-4-chloroaniline. All thermolytic reactions with

Table 1. Thermolysis of 4-halophenyl azides

Liquid reactants	Heating conditions	4-Chlorophenyl azide	**Xa**	N,N-Diacetyl-4-chloroaniline	4-Chloroacetanilide	**VIIIa**
Products, % (by gas chromatography)						
4-Chlorophenyl azide						
Acetic anhydride	S S p.v. (140 °C)[b]	0	3	76	0	21
Ac_2O/H*Ac* (2:1)[a]	S S p.v. (140 °C)[b]	0	50	50	0	0
Ac_2O/H*Ac* (1:2)[a]	S S p.v. (140 °C)[b]	0	55	15	30	0
Acetic acid	S S p.v. (140 °C)[b]	0	100	0	0	0
Acetic anhydride	Reflux (139 °C)	0	5	35	0	65
Acetic acid	Reflux (118 °C)	50	50	0	0	0
		4-Bromophenyl azide	**Xb**	N,N-Diacetyl-4-bromoaniline	4-Bromoacetanilide	**XIIIb**
4-Bromophenyl azide						
Acetic anhydride	S S p.v. (140 °C)[b]	0	3	53	0	44
Ac_2O/H*Ac* (2:1)[a]	S S p.v. (140 °C)[b]	0	10	0	0	90
Ac_2O/H*Ac* (1:2)[a]	S S p.v. (140 °C)[b]	0	100	0	0	0
Acetic acid	S S p.v. (140 °C)[b]	0	98	2	0	0
Acetic anhydride	Reflux (139 °C)	0	5	55	0	40
Acetic acid	Reflux (118 °C)	60	40	0	0	0

[a] Acetic anhydride plus acetic acid in the ratio indicated

[b] Stainless steel pressure vessel

Table 2. Thermolysis of 4-bromophenyl azide in a 1:1 mixture of acetic acid and polyphosphoric acid at 140 °C for 2 h

	Products, % (by gas chromatography)						
	Unknown 1	4-Bromophenyl azide	**Xb**	Unknown 2	**VIIb**	**IXb**	Unknown 3
Original extract	12	4	20	11	12	29	12
Original extract minus **IXb**	21	8	6	19	21	0	20
Corrected original extract	12	4	6	11	12	43	12

mixtures of acetic anhydride and acetic acid were carried out in the pressure vessels at 140 °C and are detailed in Table 1.

The products of thermolysis of 4-bromophenyl azide in the polyphosphoric acid acetic acid mixture are shown in Table 2. The gas chromatogram of this mixture indicated seven products. Among these were three unidentified materials along with 4-bromophenyl azide, **Xb, VIIb**, and **IXb**. The identities of the products were verified by cochromatographing with authentic samples. 4,4′-Dibromoazobenzene did not cochromatograph with any of the peaks in chromatograms resulting from any of the thermolytic reactions, whereas **Xa** and **Xb** were identified in every respective gas chromatogram. This is contrary to what was reported in Ref. [2]. The mixture of products observed in Table 2 is also not consistent with that reported in Ref. [3] in which yields of 68% **VIIa** and 73% of **VIIb** were claimed.

That the rearrangement of 4-halophenyl azides to 2-aminophenols takes place is certain, but the products reported in Refs. [2] and [3] to be **VIIa** and **VIIb** are not correct [13], and we have been unable to determine from this work what they might be.

At this point we would like to make another correction in the Ref. [15]. In that paper it was stated that 2-acetamido-4-bromophenyl acetate was formed while it was really the 5-bromo analogue. This was evident from the fact that under the conditions of the Skraup reaction 6-bromo-8-quinolinol was formed.

Of the compounds reported here only **IXb** has a previously published ^{1}H-NMR spectrum. These spectra could not be directly compared because of a difference in solvents used. It was noted that the separation of the chemical shifts of the ring protons as well as of the amide group was much greater in *DMSO-*d_6 used in this work than in CD_2Cl_2 [23]. This led us to compare the spectra of the more soluble **VIIb** in *DMSO-*d_6 with that in $CDCl_3$ using the same instrument. The change in spectrum matched that reported for **IXb** in CD_2Cl_2. This is consistent with $CDCl_3$ acting as a hydrogen bond breaking solvent while *DMSO-*d_6 does not act in this way.

It has been reported that the 6-halobenzoxazolones (**XVa, XVb**) [16] as well as other benzoxazolones possessed antifungal activity [17, 18]. We tested all the compounds shown in Schemes 1 and 2. Testing was carried out by serial dilutions at levels of 10^3, 10^2 and 10 μg/ml in Sabouraud dextrose broth (Difco) in shake cultures at 28 °C according to published methods [19–21]. Six fungi were employed

Table 3. Antifungal activity (μg/ml) of 2-aminophenols and derivatives in Sabouraud dextrose broth at 28 °C in shake flasks after six days (test levels 10, 10^2, 10^3 μg/ml)

No.	Compound	*A. niger*	*A. oryzae*	*M. verrucaria*	*T. viride*	*M. cirinelloides*	*T. mentagrophytes*
I	2-Aminophenol	$>10^3$	$>10^3$	10^3	$>10^3$	$>10^3$	10^3
XIIa	2-Amino-5-chlorophenol	10^3	10^3	<10	10^3	10^3	<10
XIIb	2-Amino-5-bromophenol	10^3	10^3	10^2	10^3	10^3	<10
III	2-Acetamidophenol	$>10^3$	$>10^3$	$>10^3$	$>10^3$	$>10^3$	10^3
XIa	2-Acetamido-5-chlorophenol	$>10^3$	$>10^3$	$>10^3$	$>10^3$	$>10^3$	10^3
XIb	2-Acetamido-5-bromophenol	$>10^3$	$>10^3$	$>10^3$	$>10^3$	$>10^3$	10^3
V	2-Acetamidophenyl acetate	$>10^3$	$>10^3$	$>10^3$	$>10^3$	$>10^3$	$>10^3$
VIIa	2-Acetamido-5-chlorophenyl acetate	$>10^3$	$>10^3$	$>10^3$	$>10^3$	$>10^3$	10^3
VIIb	2-Acetamido-5-bromophenyl acetate	$>10^3$	$>10^3$	10^3	10^3	10^3	10^2
II	N,N,O-Triacetyl-2-aminophenol	$>10^3$	$>10^3$	$>10^3$	$>10^3$	$>10^3$	$>10^3$
VIIIa	N,N,O-Triacetyl-5-chloro-2-aminophenol	$>10^3$	$>10^3$	10^3	10^3	$>10^3$	$>10^3$
VIIIb	N,N,O-Triacetyl-5-bromo-2-aminophenol	$>10^3$	$>10^3$	10^2	10^3	$>10^3$	10^3
VI	2-Methylbenzoxazole	10^3	10^3	10^3	10^3	10^3	10^3
Xa	6-Chloro-2-methylbenzoxazole	10^3	10^3	10^3	10^3	10^3	10^3
Xb	6-Bromo-2-methylbenzoxazole	10^3	10^3	10^3	10^3	10^3	10^3
V	2-Acetamidoanisole	$>10^3$	$>10^3$	$>10^3$	$>10^3$	$>10^3$	$>10^3$
XIa	2-Acetamido-5-chloroanisole	$>10^3$	$>10^3$	10^3	10^3	10^3	10^3
XIb	2-Acetamido-5-bromoanisole	$>10^3$	$>10^3$	$>10^3$	$>10^3$	$>10^3$	10^3
XIII	Benzoxazolone	$>10^3$	$>10^3$	<10	10^3	$>10^3$	10^3
XVa	6-Chlorobenzoxazolone	10^3	10^3	10^3	10^3	10^3	10^2
XVb	6-Bromobenzoxazolone	10^3	10^3	10^3	10^3	10^3	10^2
XIV	N-Methlybenzoxazolone	$>10^3$	$>10^3$	$>10^3$	$>10^3$	$>10^3$	10^3
XVIa	6-Chloro-N-methylbenzoxazolone	10^3	10^3	10^3	10^3	10^3	10^3
XVIb	6-Bromo-N-methylbenzoxazolone	$>10^3$	$>10^3$	$>10^3$	$>10^3$	$>10^3$	$>10^3$

which included *Aspergillus niger* (ATCC 1004), *A. oryzae* (ATCC 1101), *Myrothecium verrucaria* (ATCC 9095c), *Trichoderma viride* (ATCC 8678), *Mucor cirinelloides* (ATCC 7941), and *Trichophyton mentagrophytes* (ATCC 9127). The results are presented in Table 3.

Only three compounds were active at < 10 μg/ml (**XIIa, XIII**, *M. verrucaria*, **XIIa** and **XIIb**, *T. mentagrophytes*). Five compounds were active at 10–100 μg/ml (**VIIIb**, and **XIIb**, *M. verrucaria* and **VIIb**, **XVa** and **XVb**, *T. mentagrophytes*). The rest of the compounds were active at 100–1000 μg/ml or were not active at 1000 μg/ml.

Experimental Part

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. The purity of the compounds was established by gas chromatography and by ^{1}H-NMR at 90 or 100 MHz. The gas chromatograph was a Varian Model 1400 with a flame ionization detector to which was attached a Varian Model 20 recorder. The column employed was 5 ft. by 1/8 inch o.d., packed with 10% SE-30 on Chromosorb W, and nitrogen was used as the carrier gas. ^{1}H-NMR spectra were obtained with a Varian XL-100 or with a JEOL JNM-FX90Q spectrometer using *DMSO-d_6* as the solvent and *TMS* as the internal standard except when noted otherwise.

The following compounds used in this study were purchased from Aldrich Chemical Company: 2-aminophenol, 2-aminoanisole, 2-methylbenzoxazole and 2-benzoxazolone.

N,N,O-Triacetyl-2-aminophenol (**II**)

A solution of 54.5 g (0.5 mol) of 2-aminophenol (**I**) in 250 ml of acetic anhydride was heated under reflux for 3 h. The major part of the acetic anhydride was recovered in a rotary still and the residue was brought to dryness under a stream of air and further dried at 60 °C for 2 h. The yield of product was 112 g (95%), m.p. 75–77 °C. A sample crystallized from aqueous ethanol melted at 76–77 °C and contained no 2-acetamidophenyl acetate as determined by gas chromatography and ^{1}H-NMR (Ref. [4] m.p. 77–78 °C, yield not given). ^{1}H-NMR: $\delta = 7.4$–7.5 (m, 3-H; 4-H; 5-H; 6-H), 2.25 (s, H–CH_3COO), 2.22 (s, H–CH_3CON).

2-Acetamidophenol (**III**)

Compound **II** (118 g, 0.5 mol) was suspended in 1000 ml of water with stirring and sodium hydroxide (22 g, 0.55 mol) was added. Stirring was continued until a clear solution resulted. Decolorizing carbon was added and stirring was continued for an additional 15 min, after which the carbon was removed by filtration. The solution was adjusted to *pH* 6 with hydrochloric acid and allowed to stand under refrigeration overnight. Compound **III** was removed by filtration and dried at 80 °C overnight. The yield of compound was 69 g (96%), m.p. 206–207 °C (Ref. [6] m.p. 206–207 °C, yield not given). ^{1}H-NMR: $\delta = 9.22$ (s, H–OH), 8.85 (s, H–NH), 7.30 (m, 3-H), 6.3–6.7 (m, 4-H; 5-H; 6-H), 1.99 (s, H–CH_3CON).

2-Acetamidophenyl Acetate (**IV**)

A solution of **II** (4.7 g, 0.02 mol) in 47 ml of acetic acid was heated under refulx for 3 h. The acetic acid was removed under a stream of air and the residue was dried at 80 °C for 2 h. The product (3.9 g, 87%) melted at 121–123 °C. A sample crystallized from aqueous ethanol melted at 125–126 °C (Ref. [14] m.p. 125–126 °C, yield 40%).

To a solution of **III** (100 g, 0.66 mol) in a mixture of 100 ml of pyridine in 750 ml of acetonitrile was added acetyl chloride (54 g, 0.69 mol) dropwise with stirring at ambient temperatures. The mixture was stirred for an additional 5 min after completion of addition of the acetyl chloride. Decolorizing carbon

was added and stirring was continued for 10 min longer. The carbon was removed by filtration and the solvents were recovered in a rotary still. The residue was transferred to 1500 ml of water and stirred for 15 min. After overnight refrigeration, the product was obtained by filtration and dried in air followed by further drying at 80 °C for 2 h. The yield of compound **IV** was 115 g (91%), m.p. 123–124 °C. The sample crystallized from aqueous ethanol melted at 125–126 °C. The products were prepared by both methods were free of **II** as shown by gas chromatography and ^{1}H-NMR. ^{1}H-NMR: $\delta = 8.95$ (s, H–NH), 7.46 (m, 3-H), 6.79 (m, 4-H; 5-H; 6-H), 2.18 (s, H–CH_3COO), 1.97 (s, H–CH_3CON).

2-Acetamidoanisole (**V**)

To a mixture of **III** (11.3 g, 0.075 mol) and sodium hydroxide (3.0 g, 0.076 mol) in 45 ml of water was added methyl sulfate (9.5 g, 0.075 mol; 7.1 ml) dropwise with stirring and ice cooling. Upon completion of the addition of the methyl sulfate, the temperature was brought to 70–80 °C for 1 h. The product was obtained by filtration and slurried in 10% sodium hydroxide on the filter. It was then washed free of alkali with water and air dried. The yield was 8.2 g (66%), m.p. 86–87 °C. Recrystallization from aqueous ethanol raised the melting point to 87–88 °C. (Ref. [5] m.p. 87–88 °C, yield 100%). ^{1}H-NMR: $\delta = 9.20$ (s, H–NH), 8.04 (d, 3-H), 7.0 (m, 4-H; 5-H; 6-H), 3.82 (s, H–CH_3O), 2.10 (s, H–CH_3CON), $J_{3,4} = 8$ Hz.

2-Acetamido-5-chlorophenyl Acetate (**VIIa**)

A mixture of **IV** (48 g, 0.25 mol), *NCS* (37.4 g, 0.28 mol) in 500 ml of acetic acid was stirred at ambient temperatures for 5 days. The course of the reaction was monitored by gas chromatography. The mixture was poured into 6500 ml of water, stirred for 0.5 h, and kept under refrigeration overnight. The product was obtained by filtration, washed with water and dried in air. The yield of compound was 46 g (81%), m.p. 167–168 °C. The melting point of a sample crystallized from aqueous ethanol remained unchanged (Ref. [14] m.p. 163–164 °C, yield 73%). ^{1}H-NMR: $\delta = 9.03$ (s, H–NH), 7.56 (d, 3-H), 6.96 (d, 6-H), 6.92 (dd, 4-H), 2.12 (s, H–CH_3COO), 1.92 (s, H–CH_3CON), $J_{3,4} = 9.0$ Hz, $J_{4,6} = 2.0$ Hz. (N.B. The chemical shifts reported in Ref. [1] should be multiplied by a factor of 0.94 to match those reported here. This is due to an error in the calibration of the Varian XL-100 recorder scale).

2-Acetamido-5-bromophenyl Acetate (**VIIb**)

^{1}H-NMR: $\delta = 8.99$ (s, H–NH), 7.49 (d, 3-H), 706 (d, 6-H), 7.00 (dd, 4-H), 2.12 (s, H–CH_3COO), 1.96 (s, H–CH_3CON), $J_{3,4} = 8.0$ Hz, $J_{4,6} = 2.0$ Hz. (N.B. see note to **VIIa** above). In $CDCl_3$ the values were: $\delta = 7.69$ (s, H–NH), 6.9–7.0 (m, 3-H; 4-H; 6-H), 2.21 (s, H–CH_3COO), 2.02 (s, H–CH_3CON).

N,N,O-Triacetyl-5-chloro-2-aminophenol (**VIIIa**)

The title compound was prepared from **VIIa** in the same manner as **II** was prepared from compound **I**. The yield of product resulting from a 0.05 mol run was 12.9 g (96%), m.p. 75–78 °C. The analytical sample was prepared by crystallization from aqueous ethanol, m.p. 80–81 °C. Anal. calcd. for $C_{12}H_{12}ClNO_4$: C 53.44, H 4.49, Cl 13.15, N 5.24. Found: C 53.21, H 4.63, Cl 12.98, N 5.24. ^{1}H-NMR: $\delta = 7.3$–7.6 (m, 3-H; 5-H; 6-H), 2.23 (s, H–CH_3COO), 2.21 (s, H–CH_3CON).

N,N,O-Triacetyl-5-bromo-2-aminophenol (**VIIIb**)

Compound **VIIIb** was prepared from **VIIb** in the same manner as **II** was obtained from **I**. A 0.037 mol run yielded 11.3 g (97%) of product melting at 78–80 °C. The analytical sample was prepared by crystallization from aqueous ethanol, m.p. 80–81 °C. Anal. calcd. for $C_{12}H_{12}BrNO_4$: C 45.88, H 3.85,

Br 25.44, N 4.46. Found: C 45.58, H 3.90, Br 25.20, N 4.28. ^{1}H-NMR: $\delta = 7.29$ (d, 6-H), 7.16 (dd, 4-H), 7.07 (d, 3-H), 2.12 (s, H–CH_3COO), 2.08 (s, H–CH_3CON), $J_{3,4} = 8.0$ Hz, $J_{4,6} = 2.0$ Hz.

2-Acetamido-5-chlorophenol (**IXa**)

Compound **IXa** was prepared from **VIIa** in the same manner as **III** was prepared from **II**. A 0.13 mol reaction yielded 21.5 g (90%) of product, m.p. 188–191 °C. (Ref. [14] m.p. 189–190 °C, yield not given). ^{1}H-NMR: $\delta = 10.29$ (s, H–OH), 9.28 (s, H–NH), 7.79 (d, 3-H), 6.90 (d, 6-H), 6.81 (dd, 4-H), 2.11 (s, H–CH_3CON), $J_{3,4} = 8.5$ Hz, $J_{4,6} = 2.3$ Hz.

2-Acetamido-5-bromophenol (**IXb**)

The title compound was prepared from **VIIb** in the same manner as **III** was prepared from **II**. A 0.18 mol run yielded 39 g (94%) of product, m.p. 180–182 °C. The sample crystallized from aqueous ethanol melted at 195–197 °C (Ref. [23] m.p. 189–190 °C, yield not given). ^{1}H-NMR: $\delta = 10.10$ (s, H–OH), 9.08 (s, H–NH), 7.61 (d, 3-H), 6.90 (d, 6-H), 6.80 (dd, 4-H), 2.07 (s, H–CH_3CON), $J_{3,4} = 8.5$ Hz, $J_{4,6} = 2.3$ Hz. [Ref. [23] in CD_2Cl_2 $\delta = 9.17$ (s, H–OH), 7.56 (s, H–NH), 7.13 (d, 6-H), 6.99 (dd, 4-H), 6.87 (d, 3-H), 2.24 (s, H–CH_3CON), $J_{3,4} = 8$ Hz, $J_{4,6} = 2$ Hz].

2-Acetamido-5-chloroanisole (**XIa**)

The title compound was prepared from **IXa** in the same manner as **V** was prepared from **III**. The yield of product from a 0.06 mol run was 11 g (93%). m.p. 145–146 °C. Crystallization from aqueous ethanol did not change the melting point (Ref. [24] m.p. 142.5–143.5 °C, yield not given). ^{1}H-NMR: $\delta = 9.20$ (s, H–NH), 8.00 (d, 3-H), 7.09 (d, 6-H), 6.95 (dd, 4-H), 3.45 (s, H–CH_3O), 2.11 (s, H–CH_3CON), $J_{3,4} = 8.5$ Hz, $J_{4,6} = 2.2$ Hz.

2-Acetamido-5-bronoanisole (**XIb**)

The title compound was prepared from **IXb** in the same manner as **V** was prepared from **III**. The yield of product from a 0.05 mol run was 10.2 g (84%), m.p. 165–168 °C. A sample crystallized from aqueous ethanol melted at 167–168 °C (Ref. [25] m.p. 164–167 °C, yield not given). ^{1}H-NMR: $\delta = 9.15$ (s, H–NH), 7.89 (d, 3-H), 7.18 (d, 6-H), 7.10 (dd, 4-H), 3.86 (s, H–CH_3O), 2.10 (s, H–CH_3CON), $J_{3,4} = 8.5$ Hz, $J_{4,6} = 2.2$ Hz.

2-Amino-5-chlorophenol (**XIIa**)

Compound **IXa** (14 g, 0.075 mol) in 150 ml of hydrochloric acid was heated under reflux for 3 h, after which the solution was decolorized with carbon and adjusted to *pH* 6 to 7 with NH_4OH. After refrigerating overnight the product was removed by filtration in 8.0 g (75%) yield, m.p. 152–154 °C. Crystallization from aqueous ethanol did not change the melting point (Ref. [14] m.p. 152–153 °C, yield 75%). ^{1}H-NMR: $\delta = 9.25$ (s, H–OH), 6.65 (d, 6-H), 6.51 (m, 3-H; 4-H), 4.70 (s, H–NH).

2-Amino-5-bromophenol (**XIIb**)

The title compound was prepared from **IXb** as above. A 0.075 mol run yielded 8.0 g (75%) of product, m.p. 150 °C unchanged by crystallization from aqueous ethanol (Ref. [26] m.p. 150 °C, yield not given). ^{1}H-NMR: $\delta = 9.42$ (s, H–OH), 6.97 (d, 6-H), 6.82 (dd, 4-H), 6.69 (d, 3-H), 4.84 (s, H–NH).

2-Methyl-6-chlorobenzoxazole (**Xa**)

Compound **IXa** (18.5 g, 0.1 mol) was heated in a sublimation apparatus set in an oil bath at 230 °C until the sample melted. The bath was was allowed to cool to 175 °C, and the contents of the sublimator were placed under vacuum (0.5–1.0 mm) until the sublimation was complete. The cold finger was scraped to yield 14 g (84%) of product, m.p. 42–43 °C. On resublimation of a sample it melted at 44–45 °C (Ref. [27] b.p. 64–65 °C/13.3 Pa, yield 90%. Anal. Calcd. for C_8H_6ClNO: C 57.33, H 3.61, Cl 21.15, N 8.36. Found: C 57.03, H 3.74, Cl 20.99, N 8.08. ^{1}H-NMR: $\delta = 7.84$ (d, 7-H), 7.67 (d, 4-H), 7.37 (dd, 5-H), 2.63 (s, H–CH_3), $J_{4,5} = 8.0$ Hz, $J_{5,7} = 1.7$ Hz.

2-Methyl-6-bromobenzoxazole (**Xb**)

The preparation of **Xb** from **IXb** was carried out in the same manner as for **IXa** to **Xa**. A 0.05 mol run yielded 8 g (75%) of product melting at 45–47 °C. A second sublimation raised the melting point to 48–49 °C. Anal. calcd. for C_8H_6BrNO: C 45.31; H 2.85, Br 37.68, N 6.61. Found: C 45.21, H 2.90, Br 37.60, N 6.33, ^{1}H-NMR: $\delta = 8.16$ (d, 7-H), 7.80 (d, 4-H), 7.72 (dd, 5-H), 2.63 (s, H–CH_3), $J_{4,5} = 8.2$ Hz, $J_{5,7} = 1.2$ Hz.

6-Chlorobenzoxazolone (**XVa**)

Benzoxazolone (1.4 g, 0.01 mol) and *NCS* (1.4 g, 0.01 mol) were added to 15 ml of acetic acid and stirred for 7 days at ambient temperatures. The reaction course was monitored by gas chromatography. Upon completion of the reaction, the mixture was poured into 500 ml of water, stirred 15 min, and the product recovered by filtration. After washing with water and drying at 90 °C overnight, **XVa** was obtained in 1.6 g (94%) yield, m.p. 194–195 °C. Crystallization from aqueous ethanol did not alter the melting point (Ref. [28] m.p. 194–195 °C, yield 81%). ^{1}H-NMR: $\delta = 11.70$ (s, H–NH), 7.45 (d, 7-H), 7.21 (dd, 5-H), 7.07 (d, 4-H), $J_{4,5} = 7.87$ Hz, $J_{5,7} = 1.65$ Hz.

6-Bromobenzoxazolone (**XVb**)

The title compound was prepared from benzoxazolone (**XIII**) and *NBS* in the same manner as **XVa** was prepared. A 0.01 mol run yielded 1.4 g (67%) of product, m.p. 195–197 °C (Ref. [29], m.p. 194–196 °C, yield 70%). ^{1}H-NMR: $\delta = 11.76$ (s, H–NH), 7.56 (d, 7-H), 7.33 (dd, 5-H), 7.05 (d, 4-H), $J_{4,5} = 8$ Hz, $J_{5,7} = 2$ Hz.

N-Methylbenzoxazolone (**XIV**)

Compound **XIV** was prepared from **XIII** in the same manner as **VI** was prepared from **II**. The yield of product from a 0.0075 mol run was 1.5 g (90%), m.p. 84 °C (Ref. [30] m.p. 83–84 °C, yield not given). ^{1}H-NMR: $\delta = 7.0$–7.4 (m, 4-H; 5-H; 6-H; 7-H), 3.36 (s, H–CH_3).

6-Chloro-N-methylbenzoxazolone (**XVIa**)

The title compound was prepared by chlorination of **XV** with *NCS* in acetic acid in the same manner as **VIIa** was prepared from **IV**. The yield of product from a 0.01 mol run was (90%), m.p. 97 °C. Upon crystallization from aqueous ethanol the compound melted at 104 °C (Ref. [28] m.p. 104–105 °C, 88% yield). ^{1}H-NMR: $\delta = 7.51$ (d, 7-H), 7.28 (dd, 5-H), 7.27 (d, 4-H), 3.34 (s, H–CH_3), $J_{4,5} = 8$ Hz, $J_{5,7} = 2$ Hz.

6-Bromo-N-methylbenzoxazolone (**XVIb**)

The title compound was prepared by bromination of from **XV** with NBS in acetic acid in the same manner as **XVIa** was prepared from **XV**. The product from a 0.01 mol run was obtained in 88% yield,

m.p. 146–147 °C. Upon crystallization from aqueous ethanol **XVIb** melted at 149 °C (Ref. [31], m.p. 150 °C, no yield reported). ^{1}H-NMR: $\delta = 7.60$ (d, 7-H), 7.36 (dd, 5-H), 7.15 (d, 4-H), 3.33 (s, H–CH_3), $J_{4,5} = 9.8$ Hz, $J_{5,7} = 2.1$ Hz.

2-Acetamido-5-bromophenol (**IXb**)

The combined thermolysis mixtures of 4-bromophenyl azide (4.0 g, 0.02 mol) formed in acetic anhydride, acetic acid (2:1) and acetic acid (Table 1) were evaporated under a stream of air. The residue was dissolved in aqueous methanol and adjusted to *pH* 13 with potassium hydroxide. Decolorizing carbon was added to the clear solution and stirring was continued for 15 min. The carbon was removed by filtration and the clear liquid was acidified with hydrochloric acid. The product was obtained by filtration, washed with water and air dried. The yield of compound was 4 g (86%), m.p. 183–184 °C. Crystallization from aqueous ethanol raised the melting point to 193–194 °C, and the ^{1}H-NMR spectrum coincided with that of **IXb**.

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