2-(*o*-Hydroxyanilido)alkylnitriles *vs.* 2-[1-(*o*-Hydroxyanilido)alkyl]-benzoxazoles as Products from *o*-Aminophenol and Cyanohydrins

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The reaction of *o*-aminophenol with cyanohydrins leads to the formation of novel benzoxazoles **2** or the expected 2-(*o*-hydroxyanilido)alkylnitriles **3** or mixtures of these two, depending on the alkyl substituents on the cyanohydrin. The formation of benzoxazoles **2** was found to be due to the intrinsic instability of the corresponding 2-(*o*-hydroxyanilido)alkylnitriles, such as **4**.

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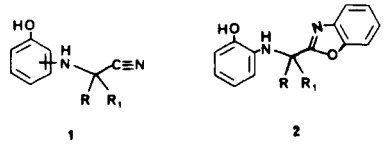
The formation of 2-(anilido)alkylnitriles from the reaction of anilines with cyanohydrins is well known [1-6]. Several hydroxylated analogs, 2-(hydroxyanilido)alkylnitriles of the type **1**, are reported to have been prepared in a similar fashion from aminophenols and cyanohydrins [7,8]. In connection with another study, we required access to compounds represented by structure **1** and were led to explore the reactions of a number of aldehyde and ketone cyanohydrins with aminophenols. We wish to report that

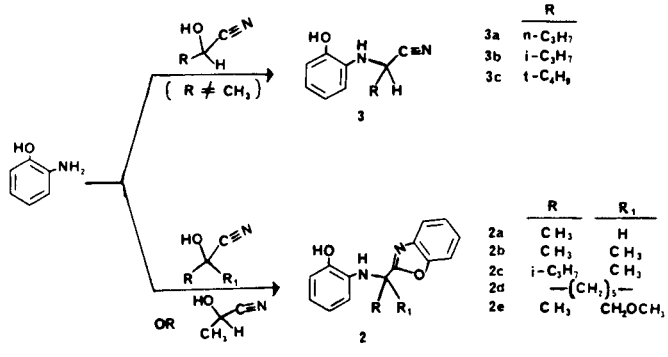


1 **2**

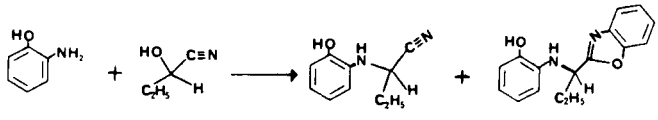
in the case of *o*-aminophenol, in addition to the expected 2-(*o*-hydroxyanilido)alkylnitriles, the hitherto unknown 2-[1-(*o*-hydroxyanilido)alkyl]benzoxazoles of the structure **2** may also be formed depending on the structure of cyanohydrins employed.

In a typical reaction, a solution of *o*-aminophenol, cyanohydrin (1.05-1.15 equivalents) and methanol (20 ml per gram of *o*-aminophenol) was heated at reflux for 24-48 hours. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between dichloromethane and 1% aqueous hydrochloric acid. The dichloromethane layer was dried over magnesium sulfate, filtered and concentrated to yield the crude product which may be purified either by recrystallization or chromatography. Under these conditions, two types of products, **2** or **3**, were formed. For example, 2-(*o*-hydroxyanilido)alkylnitriles **3a-3c** were formed from *n*-butyraldehyde cyanohydrin, isobutyraldehyde cyanohydrin or trimethylacetaldehyde cyanohydrin, whereas benzoxazoles **2a-2e** were the sole products formed from 2-hydroxypropionitrile, acetone cyanohydrin, 3-methyl-2-butanone cyanohydrin, cyclohexanone cyanohydrin, or methoxyacetone cyanohydrin, respectively (Scheme I). When propionaldehyde cyanohydrin, which is a higher homolog of 2-hydroxypropionitrile, which forms **2a**, and a lower homolog of *n*-butyraldehyde cyanohydrin,

Scheme I



Scheme II

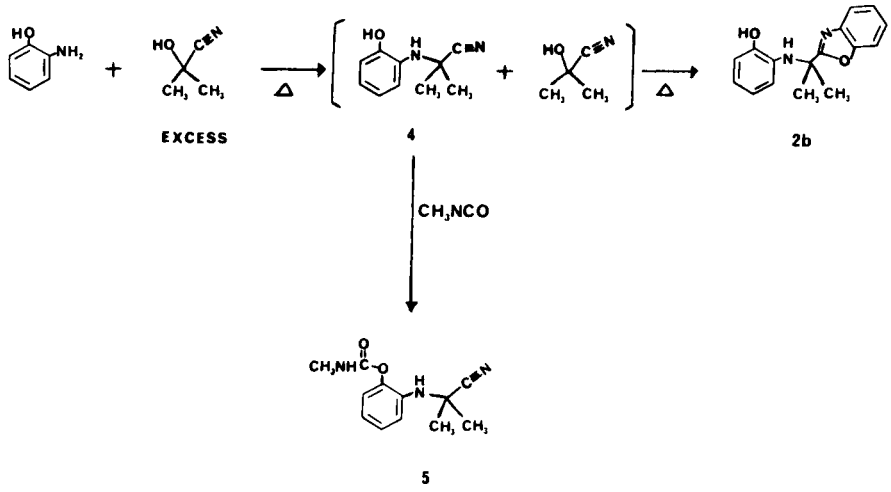


3d **2f**

which forms **3a**, was reacted with *o*-aminophenol, **3d** [9] was obtained with a very small amount of **2f** [10] (Scheme II).

In order to determine the nature of the intermediate leading to benzoxazoles **2**, experiments were conducted using *o*-aminophenol, an excess of acetone cyanohydrin (5 equivalents) and more dilute conditions (than the general condition described above) in an attempt to minimize the formation of benzoxazole **2b**. When the reaction was run for 36 hours under refluxing conditions, **2b** was the isolated product. However, when the reaction was repeated and allowed to react for only 6 hours, **13**C nmr spectrum of the crude product, after removal of methanol at room temperature, was consistent with that of a mixture of **4** and acetone cyanohydrin (Scheme III). There was no indication of the presence of **2b** in the mixture. On attempting to remove acetone cyanohydrin under reduced pressure by heating at 50-60°, the material was converted to benzoxazole **2b**. Treatment of a dichloromethane solution of **4** and acetone cyanohydrin with 1% aqueous hydrochloric acid (typical work-up procedure) or water resulted in decomposition of **4**. Because of the intrinsic instability of **4**, efforts were made to isolate and characterize its stable derivatives. Reactions of the mixture of **4** and acetone cyano-

Scheme III

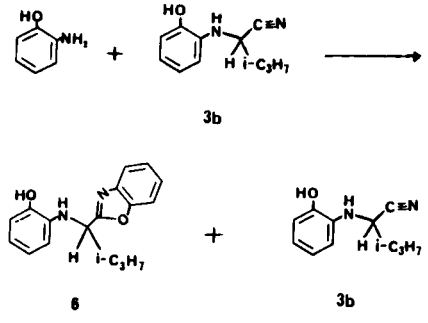


hydrin with diazomethane and with methyl isocyanate were carried out. No reaction was observed with diazomethane. However, this mixture reacted smoothly with methyl isocyanate, leading to the isolation of the *N*-methylcarbamate **5** (Scheme III). The isolation of **5** unequivocally determined the formation of **4** as an intermediate. These findings suggest that compound **4** is not very stable and in the presence of *o*-aminophenol (presumably generated from partial decomposition of **4**) it undergoes further reaction to form benzoxazole **2b**. Methacrylonitrile, which is a likely by-product, was not detected during the thermal conversion of the mixture of **4** and acetone cyanohydrin to **2b** *in vacuo*.

The hydroxy group of *o*-aminophenol appears to play an important role in influencing the stability of 2-(*o*-hydroxyanilido)alkylnitriles and, furthermore, controlling the reaction course. In the absence of the hydroxy group at the *ortho* position of anilines (*e.g.* aniline, *o*-methoxyaniline or *p*-hydroxyaniline), only the expected 2-(anilido)alkylnitriles were formed in high yields from the reactions with aldehyde or ketone cyanohydrins.

In another experiment, compound **3b** was treated with one equivalent of *o*-aminophenol in order to induce the formation of benzoxazole **6** (Scheme IV). Mass spectral

Scheme IV



and ^{13}C nmr spectral analyses of the crude reaction product indicated it to be a mixture of **3b** and **6**.

During the course of our investigation, the reaction of *o*-aminophenol and isobutyraldehyde cyanohydrin in various quantities has been repeated under similar conditions seventeen times. Compound **3b** has been the sole isolated product except for two occasions that its benzoxazole **6** was obtained. In one instance, two reactions were conducted side-by-side using *o*-aminophenol and isobutyraldehyde cyanohydrin from the same sources. One resulted in the formation of the expected **3b** and the other resulted in the isolation of **6**. It was noted that the reaction leading to **3b** remained as light red solution throughout the reaction course, however, the one leading to **6** changed from light red to light yellow and then to light red. Several attempts were made to induce the formation of **6** by adding catalytic amounts of water, or *p*-toluenesulfonic acid, or sodium carbonate or sodium hydroxide to the reaction solution. Under these conditions, however, **3b** was still obtained as the sole product. It remains unclear as to what triggered the formation of **6** on these two occasions.

In summary, except for the unexplained formation of **6** on two occasions, this brief study of reactions with *o*-aminophenol revealed that with the exception of 2-hydroxypropionitrile, 2-(*o*-hydroxyanilido)alkylnitriles (**3**) were formed from aldehyde cyanohydrins and benzoxazoles (**2**) were obtained from ketone cyanohydrins or 2-hydroxypropionitrile. The formation of benzoxazoles **2** was found to be due to the intrinsic instability of the corresponding 2-(*o*-hydroxyanilido)alkylnitriles, such as **4** [11].

EXPERIMENTAL

Compounds **2a-2e** and **3a-3d** were prepared according to the procedure described above. The melting points are uncorrected. The ^1H nmr spectra were obtained with a Varian Associates EM-360L spectrometer using tetramethylsilane as an internal stan-

dard. The ^{13}C nmr spectra were recorded at 22.5 MHz with a JEOL FX 90Q fourier transform spectrometer. Infrared spectra were recorded on a Perkin-Elmer 197 spectrometer. Analyses by high resolution mass spectrometry were obtained through a contract laboratory at Research Triangle Institute, N. Carolina. An AEI Model MS902 double focusing mass spectrometer (static resolution ~10,000) was employed.

2-[1-(*o*-Hydroxyanilido)ethyl]benzoxazole (**2a**).

A solution of *o*-aminophenol (20.0 g), 2-hydroxypropionitrile (13.7 ml) and methanol (400 ml) was refluxed under nitrogen for 30 hours. Methanol was removed *in vacuo* and the residue was dissolved with dichloromethane and 1% aqueous hydrochloric acid. The dichloromethane layer was washed with one more portion of 1% aqueous hydrochloric acid, dried over magnesium sulfate, filtered and concentrated *in vacuo* to give 9.7 g (56% yield) of a beige solid as **2a**, mp 139.5-141°; ^{13}C nmr [deuteriochloroform/(methyl sulfoxide)-d_6]: δ 168.2 (s), 150.4 (s), 144.4 (s), 140.4 (s), 135.2 (s), 124.6 (d), 124.0 (d), 119.9 (d), 119.5 (d), 117.8 (d), 114.2 (d), 111.5 (d), 110.4 (d), 47.8 (d) and 20.3 (q); ci/ms: m/e 255 ($M^+ + 1$, base peak); high resolution ms at m/e 254, 254.1052 (Calcd. for $C_{15}H_{14}N_2O_2$: 254.1055).

Anal. Calcd. for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.94; H, 5.75; N, 10.96.

2-[1-(*o*-Hydroxyanilido)-1-(methyl)ethyl]benzoxazole (**2b**).

This compound was prepared from *o*-aminophenol and acetone cyanohydrin based on the procedure for the preparation of compound **2a**, 58% yield, mp 152-155.5°; ^{13}C nmr [deuteriochloroform]: δ 171.6, 150.9, 148.7, 140.3, 132.9, 125.1, 124.5, 121.8, 120.2, 120.1, 119.8, 115.6, 110.8, 55.0 and 27.7. High resolution ms at m/e 268 (M^+), 268.1214 (Calcd. for $C_{16}H_{16}N_2O_2$: 268.1212).

Anal. Calcd. for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.58; H, 6.21; N, 10.25.

2-[1-(*o*-Hydroxyanilido)-1-(isopropyl)ethyl]benzoxazole (**2c**).

This compound was synthesized from *o*-aminophenol and 3-methyl-2-butanone cyanohydrin based on the procedure for the preparation of compound **2a**, 64% yield, mp 147.5-150.5°; ^{13}C nmr [deuteriochloroform/(methyl sulfoxide)-d_6]: δ 170.9, 150.6, 147.8, 140.0, 133.2, 124.7, 124.1, 120.3, 119.6, 119.58, 118.5, 114.9, 110.6, 60.5, 37.9, 18.3, 17.3 and 16.9.

Anal. Calcd. for $C_{18}H_{20}N_2O_2$: C, 72.94; H, 6.80; N, 9.45. Found: C, 72.70; H, 6.75; N, 9.21.

2-[1-(*o*-Hydroxyanilido)cyclohexyl]benzoxazole (**2d**).

This compound was prepared from *o*-aminophenol and cyclohexanone cyanohydrin according to Scheme I, 85% yield, mp 195-196°; ^{13}C nmr [deuteriochloroform/(methyl sulfoxide)-d_6]: δ 169.1 (s), 149.1 (s), 143.9 (s), 139.5 (s), 132.6 (s), 123.5 (d), 122.8 (d), 118.4 (d), 118.1 (d), 116.3 (d), 112.7 (d), 111.9 (d), 109.3 (d), 54.1 (s), 33.0 (t), 23.9 (t) and 20.0 (t).

Anal. Calcd. for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.53; N, 9.08. Found: C, 73.86; H, 6.58; N, 8.86.

2-[1-(*o*-Hydroxyanilido)-1-(methoxymethyl)ethyl]benzoxazole (**2e**).

This compound was synthesized from *o*-aminophenol and methoxyacetone cyanohydrin similar to **2a**, 63% yield, mp 149.0-151°; ^{13}C nmr [deuteriochloroform/(methyl sulfoxide)-d_6]: δ 168.2 (s), 150.3 (s), 146.8 (s), 140.1 (s), 132.8 (s), 124.5 (d), 123.8 (d), 119.4 (d), 119.4 (d), 119.1 (d), 116.3 (d), 114.3 (d), 110.3 (d), 77.3 (t), 58.9 (q), 57.1 (s) and 20.9 (q).

Anal. Calcd. for $C_{17}H_{18}N_2O_3$: C, 68.43; H, 6.08; N, 9.39. Found: C, 68.22; H, 6.23; N, 9.26.

2-[1-(*o*-Hydroxyanilido)(2-methyl)propyl]benzoxazole (**6**).

As reported in the text, this benzoxazole **6** was mysteriously formed in two occasions during a number of our repeated preparations of **3b** from the reaction of *o*-aminophenol and isobutyraldehyde cyanohydrin. Thus far, we have not been able to reproduce this result. A solution of *o*-aminophenol (200 g), isobutyraldehyde cyanohydrin (200 g) and methanol (4 ℓ) was refluxed for 48 hours. Methanol was removed *in vacuo* and the residue was heated with toluene (400 ml) for 5 minutes. Upon cooling, it was stored in a freezer overnight and a beige solid was formed. The solid was filtered and rinsed with a small amount of toluene; 120 g (47%) of **6** was obtained, mp 130-132°; ^{13}C nmr [deuteriochloroform]: δ 168.8, 150.6, 145.4, 139.8, 135.9, 125.1, 124.7, 120.3, 119.6, 118.6, 114.6, 112.2, 110.8, 58.5, 33.2, 19.2 and 18.8. High resolution ms at m/e 282 (M^+): 282.1367 (Calcd. for $C_{17}H_{18}N_2O_2$: 282.1368).

Anal. Calcd. for $C_{17}H_{18}N_2O_2$: C, 72.31; H, 6.42; N, 9.92. Found: C, 72.05; H, 6.64; N, 10.38.

2-(*o*-Hydroxyanilido)-3-(methyl)butyronitrile (**3b**).

A solution of *o*-aminophenol (200 g), isobutyraldehyde cyanohydrin (200 g) and methanol (41) was refluxed for 48 hours. Methanol was rmoved *in vacuo* and the residue was heated with toluene (350 ml) for 5 minutes. Upon cooling, it was stored in a freezer and a solid was formed. The solid was filtered and rinsed with a small amount of toluene; 296 g (86%) of **3b** was obtained as a solid, mp 60-61°. This reaction can also be worked up as described for the preparation of **2a**: ^{13}C nmr [deuteriochloroform]: δ 144.3 (s), 133.7 (s), 121.3 (d), 120.1 (d), 118.9 (s), 114.8 (d), 113.6 (d), 52.9 (d), 31.5 (d), 19.1 (q) and 18.3 (q). High rsolution ms at m/e 190 (M^+): 190.1106 (Calcd. for $C_{11}H_{14}N_2O_1$: 190.1106).

Anal. Calcd. for $C_{11}H_{14}N_2O_1$: C, 69.45; H, 7.42; N, 14.73. Found: C, 69.22; H, 7.38; N, 14.56.

2-(*o*-Hydroxyanilido)butyronitrile (**3a**).

This compound was prepared from *o*-aminophenol and *n*-butyraldehyde cyanohydrin similar to the preparation of **3b**, 99% yield, viscous oil; ^{13}C nmr [deuteriochloroform/(methyl sulfoxide)-d_6]: δ 144.9, 134.2, 120.1, 120.0, 119.2, 114.6, 112.1, 45.5, 35.2, 18.9 and 13.4. High resolution ms at m/e 190 (M^+): 190.1108 (Calcd. for $C_{11}H_{14}N_2O_1$: 190.1106).

Numerous attempts to obtain correct elemental analysis for the chromatography purified **3a** proved to be unsatisfactory, possibly due to instability.

2-(*o*-Hydroxyanilido)-3,3-(dimethyl)butyronitrile (**3c**).

This compound was prepared from *o*-aminophenol and trimethylacetaldehyde cyanohydrin based on the preparation of compound **3b**, 98% yield, viscous oil; ^{13}C nmr [deuteriochloroform]: δ 144.6, 134.0, 121.5, 120.3, 119.0, 114.9, 113.9, 57.1, 34.8 and 26.1; high resolution ms at m/e 204 (M^+): 204.1264 (Calcd. for $C_{12}H_{16}N_2O_1$: 204.1262).

Anal. Calcd. for $C_{12}H_{16}N_2O_1$: C, 70.55; H, 7.89; N, 13.71. Found: C, 70.92; H, 7.83; N, 13.71.

Characterization of **4** *via* its *N*-Methylcarbamate **5**.

A solution of *o*-aminophenol (3 g), acetone cyanohydrin (11.7 g, 5 equivalents) and methanol (180 ml) was heated at reflux for 6 hours. After removal of methanol *in vacuo* at room temperature,

^{13}C nmr spectrum [deuteriochloroform] of the residue indicated it to be a mixture of **4** [δ 148.6 (s), 131.0 (s), 123.3 (d), 122.6 (s), 120.6 (d), 120.2 (d), 114.7 (d), 50.3 (s) and 27.8 (q)] and acetone cyanohydrin [δ 122.9 (s), 64.9 (s) and 29.1 (q)]. High resolution mass spectrum at m/e 176 (molecular ion of **4**) suggested the molecular formula to be $C_{10}H_{12}N_2O_1$ consistent with that of **4** (measured mass: 176.0949, calculated mass: 176.0949).

This mixture of **4** and acetone cyanohydrin (2 g) was treated with methyl isocyanate (2 ml, excess), triethylamine (0.1 ml) and dichloromethane (40 ml) at room temperature. After stirring at room temperature for 14 hours, the dichloromethane solution was washed with water, 0.5% aqueous hydrochloric acid, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The solid residue (2 g) contained mainly **5** based on ^{13}C nmr spectral analysis. The *N*-methylcarbamate **5** was obtained as a crystalline solid after recrystallization (hexane and ethyl acetate), mp 107-111°; ir (dichloromethane): 3460, 1750 (s) cm^{-1}; ^{13}C nmr (deuteriochloroform): δ 154.6 (s), 140.3 (s), 136.3 (s), 126.1 (d), 122.5 (d), 122.1 (s, C≡N), 120.3 (d), 116.8 (d), 48.6 (s), 28.2 (q) and 27.8 (q, $NHCH_3$); ^1H nmr (deuteriochloroform): δ 7.28-6.80 (m, 4H), 5.20 (br, 1H, NH), 4.00 (br, 1H, NH), 2.86 (d, J = 5 Hz, $NHCH_3$, 3H) and 1.70 (s, 6H); high resolution ms at m/e 233 (M^+): 233.1162 (Calcd. for $C_{12}H_{15}N_3O_2$: 233.1164).

Anal. Calcd. for $C_{12}H_{15}N_3O_2$ (**5**): C, 61.78; H, 6.48; N, 18.01. Found: C, 61.87; H, 6.48; N, 17.99.

Acknowledgement.

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[9] Compound **3d**; ^{13}C nmr [deuteriochloroform]: δ 144.3, 133.5, 121.3, 120.2, 119.6, 114.9, 113.7, 47.6, 26.6 and 10.0; high resolution ms at m/e 176 (M^+): 176.0952 (Calcd. for $C_{10}H_{12}N_2O_1$: 176.0949).

[10] Compound **2f**; high resolution ms at m/e 268 (M^+): 268.1206 (Calcd. for $C_{16}H_{16}N_2O_2$: 268.1212).

[11] 2-(*o*-Hydroxyanilido)propionitrile (**3** with R = CH_3) was one of the examples disclosed in the Japan Patent 69 13,971 (1969); *Chem. Abstr.*, **72**, P21042s (1970). However, neither the physical data nor the method of preparation of this compound was described. Under our reaction conditions, only benzoxazole **2a** was formed from *o*-aminophenol and 2-hydroxypropionitrile.