o-Hydroxyphenylureas. Intermediates in the Urea Fusion Synthesis of 2-Benzoxazolinones

Ronald J. Nachman

Natural Products Chemistry Unit, Western Regional Research Center,
ARS-USDA, 800 Buchanan St. Berkeley, CA 94710

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o-Hydroxyphenylureas have been identified as intermediates in the urea fusion synthesis of 2-benzoxazolinones. The pyrolysis of these intermediates represents a new alternate synthesis of the benzoxazolinone ring system.

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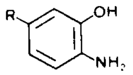
The urea fusion reaction with *o*-aminophenols or their hydrochloride salts was first described by Sandmeyer [1] in 1886 and is one of the oldest and most widely employed syntheses of the physiologically active 2-benzoxazolinones. Specifically, 6-methoxybenzoxazolinone (6-MBOA) has been reported to stimulate reproductive activity of voles and laboratory mice [2]. Furthermore, both 6-MBOA and benzoxazolinone (BOA) have been shown to inhibit seed germination [3] and numerous analogs have demonstrated analgesic and anticonvulsive properties [4]. The fusion is generally accomplished by heating an intimate mixture of either the *o*-aminophenol or the hydrochloride salt of an oxidation susceptible *o*-aminophenol with urea at 160-200° for several hours. By interrupting several urea fusion reactions conducted at the lower temperature, utilizing specifically **1a, 1b** and **1c**, we were able to isolate the respective e *o*-hydroxyphenylurea intermediates **2a** [5], **2b** and **2c**. *o*-Hydroxyphenylureas have not been previously isolated from urea fusion reaction mixtures and **2b** and **2c** are new compounds. These *o*-hydroxyphenylureas could be subsequently pyrolyzed in good yield (Table I) to the respective 2-benzoxazolinones **3a, 3b** and **3c** with loss of ammonia. Pyrolysis of *o*-hydroxyphenylureas has not been previously utilized in the synthesis of 2-benzoxazolinones. As these precursor ureas can be prepared in good yield via treatment of *o*-aminophenols with isocyanic acid [6] or silyl isocyanates [7], this represents an alternate synthetic pathway to the benzoxazolinone ring system similar to the method of Harsanyi and Tofler [4,8] utilizing *N*-(*o*-hydroxyphenyl)urethans (**4**).



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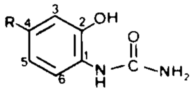

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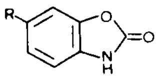

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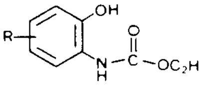
a: R=H
b: R=NO$_2$
c: R=OCH$_3$

That the *o*-hydroxyphenylureas represent true intermediates in the urea fusion reaction was confirmed by tlc analyses of samples taken at various stages of the reaction. Along with the *o*-aminophenol starting material, the appropriate *o*-hydroxyphenylurea appeared within several minutes of the start of the reaction as the only other detectable compound in the reaction mixture, followed by the appearance and gradual accumulation of the benzoxazolinone product. Within 90 minutes, the *o*-hydroxyphenylurea diminished to only a very minor component of the reaction mixture.

Another minor component that revealed a parent ion at m/z 195 in the mass spectrum was isolated from the urea fusion reaction mixture of *o*-aminophenol (**1a**). The proton nmr spectrum proved similar to **2a** but contained an additional heteroatom proton signal and in the carbon nmr spectrum two carbonyl groups at 156.7 and 153.3 ppm were observed. In addition, positive color tests for a phenolic hydroxyl were obtained with the reagents ferric chloride and bromine water [9]. This and other spectroscopic evidence suggested the biuret structure **5** [10]. While this compound has been previously synthesized, only the pmr and limited ir spectral data was reported, and the more thorough characterization described above was required to adequately determine the structure.

As biuret is produced when urea is heated [11], **5** may have resulted from the fusion [12] of *o*-aminophenol (**1a**) with biuret formed *in situ*. In a test of the viability of this hypothesis, a fusion of *o*-aminophenol with biuret was conducted from which a low yield of **5** was indeed obtained. Biuret **5** may alternatively have resulted from the condensation of **2** with isocyanic acid formed *in situ* [6,11].



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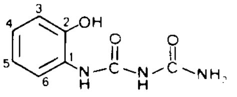

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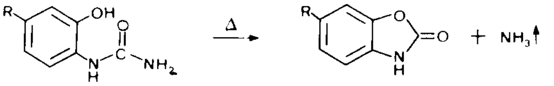
In conclusion, *o*-hydroxyphenylureas are intermediates in the urea fusion reaction of *o*-aminophenols to benzoxazolinones and their pyrolysis represents a viable alternative synthetic pathway to members of the useful benzoxazolinone ring system.

Table I

Benzoxazolinones *via* Pyrolysis of *o*-Hydroxyphenylureas



o-Hydroxyphenylurea	Benoxazolinone (% yield)
2a	**3a** (81%)
2b	**3b** (78%)
2c	**3c** (55%)

EXPERIMENTAL

The cmr, pmr, ir, uv and mass specra were obtained using a JEOL JNM-PFT-100 (100 MHz), Nicolet 200 (200 MHz), Perkin-Elmer 727-B, Cary 15 and a Micromass 7070F spectrometer respectively. Both cmr and pmr were determined in deuterioacetone unless otherwise indicated and chemical shifts are reported relative to internal tetramethylsilane. A multiplicity separation pulse sequence was employed when cmr spectra were obtained which distinguishes quaternary and methylene from methyl and methine carbons [13]. Melting points are uncorrected.

o-Hydroxyphenylurea (**2a**).

o-Aminophenol [14], **1a** (10 g, 91.7 mmoles), was thoroughly mixed with finely ground urea (10 g, 166.7 mmoles) and heated at 160° for 25 minutes. The melt was allowed to cool and was extracted with 4*M* hydrochloric acid solution (5 x 70 ml). This purple acidic solution was in turn extracted with ether (6 x 50 ml). The residue resulting from evaporation of the dried ether layer was taken up in boiling methanol, decolorized, and the product allowed to crystallize. A total of 520 mg (4%) of crystalline **2a** was collected and recrystallized from methanol as colorless needles, mp 153-154.7° (with ammonia evolution); pmr: δ 6.08 (br s, deuterium oxide exchangeable, 2H, -CONH_2), 6.74 (m, $J_{5\text{-}6}$ = 8.0 Hz, $J_{5\text{-}4}$ = 7.8 Hz, $J_{5\text{-}3}$ = 2.3 Hz, H-5), 6.89 (m, 2H, H-4 and H-3), 7.34 (dd, $J_{6\text{-}5}$ = 8.0 Hz, $J_{6\text{-}4}$ = 1.7 Hz, 1H, H-6), 8.11 (br s, deuterium oxide exchangeable, 1H, -NHCO-), 9.90 (br s, deuterium oxide exchangeable, 1H, -OH); cmr (15): δ 159.0 (-NHCONH$_2$), 148.7 (C-2), 128.4 (C-1), 124.8 (C-4), 121.8 (C-5), 120.4 (C-6), and 118.2 (C-3); uv (95% ethanol): λ max 237 and 282 nm; ms: m/z (relative intensity) 152 (M^+, 5), 135 (M^+-NH$_3$, 100), 109 (M^+-HNCO, 36), 91 (20); ir (potassium bromide): ν max (cm^{-1}) 3425 and 3320 (N-H stretching), 1620 (C=O stretching), 1590 and 1523 (N-H bending), 725 (aromatic C-H bending).

Anal. Calcd. for $C_7H_8N_2O_2$: C, 55.26; H, 5.30; N, 18.41. Found: C, 55.4; H, 5.37; N, 18.4.

The above urea fusion was repeated with an extended reaction time (2 hours) and samples for silica gel tlc analysis were removed at 5, 10, 15, 30, 60 and 90 minutes after its initiation. The intermediate urea **2a** (R_f = 0.58, acetone) appeared at 5 minutes and the benzoxazolinone **3a** (R_f = 0.67, acetone) at 15 minutes. By 90 minutes the intermediate **2a** remained as only a minor component of the reaction mixture.

4-Nitro-2-hydroxyphenylurea (**2b**).

5-Nitro-2-aminophenol [16], **1b** (10 g, 64.9 mmoles), was thoroughly mixed with finely ground urea (7 g, 118.0 mmoles) and heated at 160° for 20 minutes. Workup was identical to that used with **2a** above. A total of 210 mg (1.7%) of crystalline **2b** was collected and recrystallized from methanol as pale yellow needles, mp 196° dec; pmr: δ 6.58 (br s, deuterium oxide exchangeable, 2H, -CONH_2), 7.62 (d, $J_{3\text{-}5}$ = 2.6 Hz, 1H, H-3), 7.70 (dd, $J_{5\text{-}6}$ = 9.0 Hz, $J_{5\text{-}3}$ = 2.6 Hz, 1H, H-5), 8.32 (d, $J_{6\text{-}5}$ = 9.0 Hz, 1H, H-6), 8.51 (br s, deuterium oxide exchangeable, 1H, -NHCO-), 10.97 (br s, deuterium oxide exchangeable, 1H, -OH); cmr [15] (deuteriodimethylsulfoxide): δ 155.4 (-NHCONH$_2$), 144.9 (C-2), 140.1 (C-4), 136.2 (C-1), 116.2 (C-6 or C-5), 115.9 (C-5 or C-6) and 108.4 (C-3); ms: m/z (relative intensity) 197.0451 [Calcd for $C_7H_7N_3O_4$: 197.0436] (M^+-NH$_3$, 100), 154.0267 (180-NO$_2$, 90), 134.0241 (18); ir (potassium bromide): ν max (cm^{-1}) 3440 and 3340 (N-H stretching), 1643 (C=O stretching), 1592 and 1500 (N-H bending).

Anal. Calcd. for $C_7H_7N_3O_4$: C, 42.64; H, 3.58; N, 21.32. Found: C, 42.49; H, 3.52; N, 21.17.

The above urea fusion was repeated with an extended reaction time (2 hours) and samples for silica gel tlc analysis were removed as described for **2a**. The intermediate urea **2b** appeared at 5 minutes (R_f = 0.68, acetone) and the benzoxazolinone **3b** (R_f = 0.62, acetone) at 10 minutes. By 60 minutes the intermediate **2b** remained as only a minor component of the reaction mixture.

4-Methoxy-2-hydroxyphenylurea (**2c**).

Dry 5-methoxy-2-aminophenol hydrochloride [17] (10 g, 57.0 mmoles) was thoroughly mixed with finely ground urea (6.2 g, 103 mmoles) and heated at 160° for 25 minutes. Workup was the same as that used with **2a** above. A total of 180 mg (2%) of crystalline **2c** was collected and recrystallized from methanol as colorless needles, mp 165.2-166.1° (with ammonia evolution); pmr: δ 3.71 (s, 3H, -OCH_3), 5.88 (br s, deuterium oxide exchangeable, 2H, -CONH_2), 6.34 (dd, $J_{5\text{-}6}$ = 8.7 Hz, $J_{5\text{-}3}$ = 2.8 Hz, 1H, H-5), 6.42 (d, $J_{3\text{-}5}$ = 2.8 Hz, 1H, H-3), 6.96 (d, $J_{6\text{-}5}$ = 8.7 Hz, 1H, H-6), 7.97 (br s, deuterium oxide exchangeable, 1H, -NHCO-), 10.30 (s, deuterium oxide exchangeable, 1H, -OH); cmr [15]: δ 159.4 (-NHCONH$_2$), 158.3 (C-4), 150.7 (C-2), 123.0 (C-6), 121.6 (C-1), 105.8 (C-5), 104.5 (C-3) and 55.5 (-OCH$_3$); ms: m/z (relative intensity) 182.0688 [Calcd for $C_8H_{10}N_2O_3$: 182.0691] (M^+, 34), 165.0413 (M^+-NH$_3$, 50), 139.0639 (M^+-HNCO, 66), 124.0389 (139-CH$_3$, 100); ir (potassium bromide): ν max (cm^{-1}) 3498, 3360 and 3130 (N-H stretching), 1650 (C=O stretching), 1622 and 1550 (N-H bending).

Anal. Calcd. for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.52; H, 5.52; N, 15.24.

The above urea fusion was repeated with an extended reaction time (2 hours) and samples for silica gel tlc analysis were removed as described for **2a**. The intermediate urea **2c** (R_f = 0.61, acetone) appeared at 5 minutes and the benzoxazolinone **3c** (R_f = 0.71, acetone) at 15 minutes. By 90 minutes the intermediate **2b** remained as only a minor component of the reaction mixture.

Pyrolyses of *o*-Hydroxyphenylureas **2a**, **2b** and **2c**.

Dry *o*-Hydroxyphenylurea **2a**, **2b** or **2c** (0.6 mmole) was placed in a flask equipped with drying tube and heated at 160° for 15 minutes (**2a**), 180° for 60 minutes (**2b**), or 165° for 30 minutes (**2c**). The cooled melts were dissolved in hot methanol, decolorized and the products allowed to crystallize. The respective yields of **3a**, **3b** and **3c** were 81%, 78% and 55%. The products **3a** and **3c** were recrystallized from dichloromethane as colorless needles and **3b** from methanol as pale yellow needles. The mp, ir, pmr and cmr spectra of the products matched those reported in the literature [18,19] and their silica gel tlc R_f values (acetone eluent) were identical with those of authentic samples [18].

N-(*o*-Hydroxyphenyl)biuret (**5**).

Dry *o*-aminophenol hydrochloride (10 g, 68.8 mmoles) was mixed with finely ground urea (7.5 g, 125 mmoles) and heated at 175° for 2 hours. The cooled residue was extracted with five, 50 ml portions of 4*M* hydrochloric acid solution. This purple, acidic solution was extracted with eight, 50 ml portions of ether and the residue from the evaporation of the ether layer was dissolved in hot water, filtered and allowed to cool until a precipitate formed. The red precipitate was collected, dried, decolorized and crystallized from dichloromethane. Four crops of crystalline 2-benzoxazolinone (4.5 g, 49%) were collected followed by one crop of crystalline *o*-hydroxyphenylurea (117 mg, 1%). The supernatent was evaporated and the residue crystallized from methanol to give 48 mg of crystalline **5** (0.4%) which recrystallized from methanol as colorless needles, mp 170.5-171.5°; pmr: δ 6.48 (br s, deuterium oxide exchangeable, 2H,

-CON*H*$_2$), 6.83 (m, $J_{5\text{-}6}$ = 8.3 Hz, $J_{5\text{-}4}$ = 6.5 Hz [20], $J_{5\text{-}3}$ = 1.8 Hz [20], 1H, H-5), 6.91 (m, $J_{3\text{-}4}$ = 8.0 Hz, $J_{3\text{-}5}$ = 1.8 Hz [20], $J_{3\text{-}6}$ = 0.3 Hz [20], 1H, H-3), 6.91 (m, $J_{4\text{-}3}$ = 8.0 Hz, $J_{4\text{-}5}$ = 6.5 Hz [20], $J_{4\text{-}6}$ = 1.0 Hz [20], 1H, H-4), 7.96 (m, $J_{6\text{-}5}$ = 8.3 Hz $J_{6\text{-}4}$ = 1.0 Hz [20], $J_{6\text{-}3}$ = 0.3 Hz [20], 1H, H-6), 8.59 (br s, deuterium oxide exchangeable, 1H, -N*H*CO-), 8.97 (br s, deuterium oxide exchangeable, 1H, -CON*H*CO-), 10.29 (br s, deuterium oxide exchangeable, 1H, -O*H*), the pmr spectrum in deuteriodimethylsulfoxide was very similar to that reported in the literature [10]; cmr [15]: δ 156.7 (-NH*C*ONH$_2$), 153.3 (-NH*C*ONH-), 147.5 (C-2), 127.6 (C-1) 124.4 (C-4), 121.3 (C-5), 120.5 (C-6) and 116.2 (C-3); ms: m/z (relative intensity) 195.0642 [Calcd for $C_8H_9N_3O_3$: 195.0644] (M^+, 20), 178.0378 (M^+-NH_3, 9), 135.0326 (M^+-$(NH_2)_2CO$, 67), 109.0536 (100), and for comparison, biuret ms: 103 (M^+, 7) 60 (M^+-HNCO, 98), 44 (78), 43 (M^+-$(NH_2)_2CO$, 100); uv (95% ethanol): λ/max 243 and 284 nm; ir (potassium bromide): ν/max (cm^{-1}) 3448, 3330 and 3170 (N-H stretching), 1690 (C=O stretching) (lit [10] 1720-1690), 1587 and 1535 (N-H bending), 735 (aromatic C-H bending).

Anal. Calcd. for $C_8H_9N_3O_3$: C, 49.23; H, 4.65; N, 21.53. Found: C, 49.08; H, 4.72; N, 21.29.

Qualitative phenol tests were performed on **5** and for comparison purposes on **2a**, **3a** and biuret with the reagent solutions ferric chloride [9], bromine water [9] and cerric nitrate [21]. Compounds **5** and **2a** demonstrated positive responses (brown to black precipitates) to the tests while **3a** demonstrated negative responses to the first two tests but a positive response to the ceric nitrate test. As expected, biuret demonstrated negative responses to all of the tests.

Biuret Fusion (12) Synthesis of *N*-(*o*-Hydroxyphenyl)biuret (5).

o-Aminophenol, **1a** (10 g, 91.7 mmoles), was thoroughly mixed with biuret [14] (10 g, 97.1 mmoles) and heated at 175° for 20 minutes. The melt was allowed to cool and extracted with 4*M* hydrochloric acid solution (5 × 70 ml). The acidic solution was extracted with dichloromethane (6 × 100 ml) and the organic layer was dried, evaporated and the resulting residue taken up in boiling methanol. This solution was decolorized and allowed to cool until crystallization of **5** occured. A total of 1.4 g of crystalline **5** (8%) was collected and recrystallized from methanol as plates. The original supernatant yielded 485 mg (4%) of crystalline 2-benzoxazolinone (**3a**) as well. No attempt was made to maximize the yield of **5**. The product **5** of this reaction was found to be identical with the sample isolated from the urea fusion of **2a** (pmr, ir, cmr, and tlc).

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REFERENCES AND NOTES

[1] T. Sandmeyer, *Chem. Ber.*, **19**, 2655 (1886).

[2] E. H. Sanders, P. D. Gardner, P. J. Berger, and N. C. Negus, *Science*, **214**, 67 (1981).

[3] G. F. Nicollier, P. A. Hedin, and F. M. Davis, *J. Agric. Food Chem.*, **30**, 1133 (1982).

[4] J. Sam, and J. L. Valentine, *J. Pharm. Sci.*, **58**, 1043 (1969).

[5] It is interesting to note that *o*-hydroxyphenylurea (**2a**) has been reported to demonstrate cytokinin activity; H. Iwamura, T. Fujita, S. Koyama, K. Koshimizu, and Z. Kumazawa, *Phytochemistry*, **19**, 1309 (1980).

[6a] D. Simov, and V. Kalcheva, *C. R. Acad. Bulgare Sci.*, **17** (9), 825 (1964); *Chem. Abstr.*, **61**, 15996b (1964); [b] M. F. Zienty, U. S. Patent 2,967,775, Jan. 10, 1961., *Chem. Abstr.*, **55**, 6726c (1961).

[7] V. P. Kozyukov, E. B. Muzovsky and B. F. Mironov, *Zh. Obshch. Khim.*, **50**, 1425 (1980); *Chem. Abstr.*, **93**, 186451w (1980).

[8] K. Harsanyi and F. Toffler, *Ann. Chim.* (Rome), **54**, 1066 (1964); *Chem. Abstr.*, **62**, 11796g (1965).

[9] D. J. Pasto, and C. R. Johnson, ed, "Organic Structure Determination", Prentice-Hall, Englewood Cliffs, NJ, 1969, p 369.

[10] J. J. Bour, J. H. M. van de Brugh Arts, H. M. J. Hendriks and J. J. Steggarda, *Rec. Trav. Chim.*, **96**, 125 (1977).

[11] F. Kurzer, *Chem. Rev.*, **56**, 95 (1956).

[12] F. Kurzer, *ibid.*, **56**, 110 (1956).

[13] C. Le Cocq and J. Y. Lallemand, *Chem. Commun.*, 150 (1981).

[14] Purchased from Aldrich Chemical Co., Inc.

[15] Cmr assignments are based on the table of additive mono-substituted benzene substituent chemical shift parameters in: D. F. Ewing, *Org. Magn. Reson.*, **12**, 49 (1979).

[16] Purchased from ICN Pharmaceuticals, Inc.

[17] E. H. Allen and S. K. Laird, *J. Org. Chem.*, **36**, 2004 (1971).

[18] R. J. Nachman, *J. Heterocyclic Chem.*, **19**, 1545 (1982).

[19] R. L. Clark, and A. A. Pessalano, *J. Am. Chem. Soc.*, **80**, 1662 (1958).

[20] These coupling constants were determined with a Nicolet spectral simulation program written for a Nicolet 1180 computer.

[21] R. L. Shriner, R. C. Fuson, and D. T. Curtin, "The Systematic Identification of Organic Compounds", John Wiley and Sons, Inc. 1968, p 124.