Short Communication

Oxidation of β-Blocking Agents. Part IV. Oxidation of Propranolol and its Glycol with *N*-Bromosuccinimide

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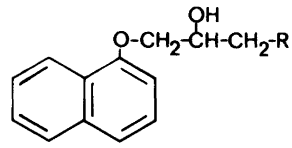
Since its discovery in 1964, propranolol [1-(isopropylamino)-3-(1-naphthoxy)-2-propanol] (**1**, Scheme 1) has been widely used in therapy, despite the subsequent introduction of several other β-adrenergic blocking drugs. **1** is metabolized by several oxidation pathways in which the major metabolites are 4-hydroxypropranolol [1-(isopropylamino)-3-(4-hydroxy-1-naphthoxy)-2-propanol], *N*-desisopropylpropranolol [1-amino-3-(1-naphthoxy)-2-propanol], α-naphthol, propranolol glycol [1-(1-naphthoxy)-2,3-propylene glycol] (**2**, Scheme 1), α-naphthoxylactic acid and α-naphthoxyacetic acid. The metabolic conversion of **1** to **2** proceeds through the intermediate 3-naphthoxy-2-hydroxypropionaldehyde. The aldehyde is either reduced to **2** or oxidized to the acidic products mentioned above.[1]



Scheme 1.

In an earlier study on β-blockers in which sodium metaperiodate was used as oxidizing agent, α-naphthoxyacetaldehyde was identified as the main decomposition product of **1** and **2**.[2] In the present study the effect of *N*-bromosuccinimide (NBS) on **1** and **2** has been investigated. NBS was selected for study because it is an effective oxidizing agent for alcohols and ethers,[3,4] and because contradictory results have been reported in the literature regarding the products of its reaction with **1**.[5,6]

1 and **2** were readily oxidized by NBS in acidic and neutral solution. TLC studies of the oxidation mixtures revealed several spots other than those for **1**, **2** and NBS, but none of them corresponded to α-naphthoxyacetaldehyde, the major product in $NaIO_4$ oxidation.[2] The products obtained depended on the reaction conditions. By changing the composition of the reaction solution it was possible to obtain good yields of each of the products in turn. Mercuric acetate was added to the oxidation mixture in Method 1 to prevent the bromination of the products by the formation of $HgBr_4^{2-}$,[7] but it had no effect on the side reaction. NBS was used in excess. If more **1** was used than NBS, or if the oxidation was carried out in alkaline solution, reactions were extraordinarily slow and the amounts of the oxidation products were too small to isolate. The solutions were examined only by TLC.

In the present study the oxidations were carried out in solutions protected from light. The influence of light on the oxidation reaction will be discussed in a forthcoming paper (Part V).

1 and **2** yielded the same products when they were oxidized with NBS. However, the solubility of the glycol in the solvent systems was poorer

than that of propranolol hydrochloride, even when the mixture was heated. Four major components, tentatively referred to as compounds **3**–**6**, were isolated from the oxidation solutions, though the presence of trace amounts of closely related compounds made their purification difficult. The structures of the oxidation products were studied by spectroscopic methods.

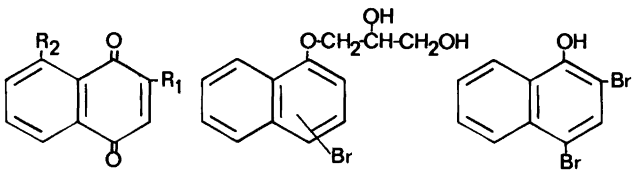
Compound **3** was the most abundant degradation product (yield about 40 %) in the acidic oxidation solution containing mercuric acetate. Freshly crystallized **3** was reddish brown but it darkened on standing. Storage in a refrigerator retarded the darkening. The deep red spot of **3** on the TLC plate after 2,4-dinitrophenylhydrazine (2,4-DNPH) visualization, and the greyish colour after Folin-Ciocalteu visualization were clear indications of the carbonyl moiety and the phenolic OH group, respectively. The doublet band at 1675, 1660 cm^{-1} and the broad absorption at about 3490 cm^{-1} in the IR spectrum confirmed the presence of C=O and OH groups, respectively. The absence of the absorption just below 3000 cm^{-1} showed that the side chain of **1** was replaced by a carbonyl function.

The naphthoquinone structure of **3** was verified by the NMR spectra. Signals for carbonyl carbons were observed at δ 178.7 and 178.0 ppm in the ^{13}C NMR spectrum, consistent with the data available on naphthoquinones.[8] All other signals were also found in the unsaturated region. The ^1H NMR spectrum showed a one-proton singlet at δ 7.08 ppm, due to the proton of the quinonoid ring, and a complex pattern at δ 8.2–7.7 ppm, due to the three adjacent benzenoid protons. The broad one-proton signal at about δ 5.9–5.4 ppm was apparently produced by the OH group. This was verified by recording the spectrum in DMSO-d_6 and observing the disappearance of the signal upon shaking with D_2O.

The molecular ion at *m/z* 252 formed the base peak in the mass spectrum of **3**. The typical isotope peak *M*+2 showed the substitution of bromine for one proton and the formula $C_{10}H_5BrO_3$ was deduced for the molecular ion. The abundant peak found at *m/z* 105 is highly characteristic for naphthoquinones containing C_2 or C_3 hydroxy substituents.[9] Compound **3** was concluded to be a 1,4-naphthoquinone on the basis of the intensity of the molecular peak. The fragmentation of bromine (*M*-79) was evident. The peaks at *m/z* 145, 117, 105, 89, 77, 63 and 50 were identical with the peaks appearing in the fragmentation of 2- and 3-hydroxy-1,4-naphthoquinone.[9] From the data available it was impossible to conclude whether the OH group was at the C_2 or C_3 position in the quinonoid ring.

The position of the bromine substituent in the benzenoid ring was either C_5 or C_8 according to the ^1H NMR spectrum of **3**, which showed the complex signal for the three adjacent protons. The chemical shifts of **3** differed from those calculated for 2-bromo-5-hydroxy- and 2-bromo-8-hydroxy-1,4-naphthoquinones. 8-Bromo-2-hydroxy-1,4-naphthoquinone (8-bromolawsone) has been described in the literature, but its structure was incompletely determined.[10] The IR and melting point data and the unstable character of **3** were all in agreement with the information available for 8-bromolawsone. On the basis of the data available, **3** is suggested to be 8-bromo-2-hydroxy-1,4-naphthoquinone (Scheme 2).

Compound **4** was the major product (yield about 80%) in the acidic oxidation solution not containing mercuric acetate. Positive reaction with 2,4-DNPH on the TLC plate and the carbonyl absorption with two bands in the IR spectrum suggested that, like **3**, compound **4** was a naphthoquinone. The *M*+2 isotope peak in the mass spectrum showed the presence of one brom-



	R_1	R_2
3	OH	Br
4	Br	H

5 **6**

Scheme 2.

Table 1. ^{13}C NMR chemical shift data (ppm) for **4** and **6** (s = singlet, d = doublet).

Carbon	**4**	Lit.[a]	**6**	Lit.[b]
C_1	177.8 s	177.7	148.1 s	148.0
C_2	140.1 s	140.0	103.1 s	103.1
C_3	140.3 d	140.5	131.0 d	131.0
C_4	182.4 s	182.2	113.3 s	113.2
C_5	126.9 d	126.9	127.1 d	127.0
C_6	134.1 d	134.0	128.1 d	128.0
C_7	134.4 d	134.4	126.8 d	126.7
C_8	127.8 d	127.8	122.7 d	122.6
C_9	131.7 s	131.8	131.8 s	131.7
C_{10}	130.9 s	131.0	125.1 s	125.0

[a]Ref. 11. [b]Ref. 13.

ine substituent. The molecular ion at *m/z* 236 was abundant and corresponded to the formula $C_{10}H_5BrO_2$. The ^1H and ^{13}C NMR spectra of **4** were identical with those of 2-bromo-1,4-naphthoquinone[8,11] (^{13}C NMR data in Table 1), and it was concluded that **4** is 2-bromo-1,4-naphthoquinone (Scheme 2).

Compound **5** was isolated in only trace amounts. The intense absorption in the aliphatic C-H stretching region below 3000 cm^{-1} in the IR spectrum and the strong absorption in the OH region at about 3300 cm^{-1} suggested that **5** contained an aliphatic side chain and the OH group. The IR spectrum was very much like that of **2**. In the mass spectrum, the molecular ion peak appeared at *m/z* 296 and the isotope peak of bromine *M*+2 was observed. From this it seemed clear that **5** is brominated **2**, i.e. $C_{13}H_{13}BrO_3$. This was confirmed by the elemental analysis. Because the amount of **5** was insufficient to record the NMR spectra, the exact position of the bromine substituent in the ring system could not be determined. Presumably **5** is brominated 1-(1-naphthoxy)-2,3-propylene glycol (Scheme 2).

Compound **6** was the main product (yield about 65%) in the neutral oxidation solution. The spot on the TLC plate did not change colour when sprayed with 2,4-DNPH but turned greyish blue with Folin-Ciocalteu reagent, indicating the presence of a phenolic OH group. The absorption of the OH group in the IR spectrum was distinct at about 3420 cm^{-1}. The lack of an aliphatic moiety confirmed the cleavage of the ether linkage in propranolol. The molecular ion peak appeared at *m/z* 300 in the mass spectrum. The molecular ion cluster indicated the presence of two bromine substituents, the *M*+2 peak being the base peak of the spectrum. The formula $C_{10}H_6Br_2O$ for the molecular ion was confirmed by elemental analysis and by ^1H and ^{13}C NMR spectra. The NMR spectra were consistent with those of 2,4-dibromo-1-naphthol reported in the literature[12,13] (^{13}C NMR data in Table 1) and with the spectra of a reference sample of 2,4-dibromo-1-naphthol synthesized in the laboratory. Compound **6** was thus identified as 2,4-dibromo-1-naphthol (Scheme 2).

The results showed that the ether linkage of **1** and **2** is more readily oxidized by NBS than the alcoholic function of the compounds. Under the acidic conditions, the formation of 1,4-naphthoquinones was favoured, whereas in the neutral solution the reaction stopped at the naphthol stage. The role of mercuric acetate is noteworthy: It could not prevent the bromination of the products, but in its presence the oxidation proceeded further to give a hydroxylated naphthoquinone. The only compound also found among the metabolic products was 1-naphthol, but it contained two bromine substituents in the present study.

According to the literature, **1** is oxidized to a ketone[5] and to 2,4-dibromo-α-naphthoxyacetaldehyde.[6] Neither of these compounds was detected in the present study, even when the oxidation was carried out under the conditions described in the literature. The oxidation conditions were modified in the present study to facilitate the isolation process, which was otherwise difficult.

1 is oxidized by a variety of reagents, but in our experience it is stable towards oxidation under normal storage conditions. Contact of **1** with oxidizing agents should be avoided.

Experimental

1 as the hydrochloride was kindly supplied by Leiras Pharmaceutical Company (Finland). **2** was synthesized by the method described for mephenesin.[14] The identity and purity of the substances were verified by TLC and by UV, IR and ^1H NMR spectra. All other reagents and solvents were of analytical grade.

Elemental analyses were performed by Ilse Beetz Microanalytical Laboratory (West Germany). Melting points were determined with a Gallenkamp MF apparatus and are uncorrected.

The UV spectra were recorded using a Varian Techtron Model 635 spectrophotometer and the IR spectra using a Unicam SP3-200 instrument. The 200 MHz ^1H and ^{13}C NMR spectra were recorded on a Jeol JMN-FX 200 FT spectrometer using TMS as internal standard, and the mass spectra were obtained with a Finnigan Mat 8200 spectrometer (at 70 eV) with direct inlet. TLC experiments were carried out using pre-coated 0.25 mm silica gel glass or aluminium 60 F_{254} plates. The solvent systems used were dichloromethane (A), toluene – diethyl ether – acetone (88:10:5) (B), n-hexane – acetone (1:1) (C) and dichloromethane – methanol – 25 % ammonia (85:14:1) (D). The spots were detected under UV light (254 nm) and by spraying with Folin-Ciocalteu reagent or 2,4-DNPH in 2 M HCl.

The oxidation of **1** and **2** was carried out under the following conditions:

Method 1. Fifty ml of 0.1 M NBS in 10 % acetic acid solution was added to 50 ml of a 0.05 M solution of **1** as the hydrochloride or **2** containing 0.2 M mercuric acetate in 10 % acetic acid, and the reaction was allowed to proceed to completion. The reddish brown reaction mixture was then extracted with petroleum ether (b.p. 40–60 °C). Evaporation of the extract to dryness and examination by TLC showed it to contain one major compound (**3**) and several compounds in trace amounts, among them **4**, **5** and **6**. The residue was purified by flash chromatography[15] with ethyl acetate – petroleum ether (16:84) as eluent and crystallized from ethanol by adding a few drops of water (compound **3**).

Method 2. The oxidation was carried out as in Method 1 but without mercuric acetate. A yellow precipitate began to form almost immediately and it was filtered off the next day and recrystallized from water (compound **4**). The filtrate was extracted with petroleum ether and the extract was evaporated to dryness and studied by TLC. Besides the major compound **5**, the TLC plate showed traces of **3**, **4** and some unidentified products. The residue was crystallized from ethanol – water (compound **5**).

Method 3. Fifty ml of 0.1 M NBS in water was added to 50 ml of a 0.05 M aqueous solution of **1** as the hydrochloride or **2**. A grey precipitate formed almost immediately and was filtered off the following day (compound **6**).

8-Bromo-2-hydroxy-1,4-naphthoquinone (**3**). Reddish brown crystals from EtOH-H_2O. M_r 253.0, m.p. 184–186 °C (lit.[10] m.p. 185–187 °C). Found: C 50.09; H 2.16; Br 30.97. Calc. for $C_{10}H_5BrO_3$: C 47.47; H 1.98; Br 31.58. TLC, R_f values: 0.36(A), 0.51(B), 0.57(C), 0.79(D). UV λ_{max} in EtOH: 280–72 ($\varepsilon = 6375$), 253–51 ($\varepsilon = 21050$), 250–49 ($\varepsilon = 21200$) nm. IR ν_{max} (KBr disc): 3490(OH), 3070, 1675, 1660 (C = O), 1590, 1560, 1328, 1300, 1250, 970, 915, 768, 710, 655 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 8.2–7.7 (m, 3H), 7.08 (s, 1H), 5.9–5.4 (broad s, 1H, OH) ppm. ^{13}C NMR ($CDCl_3$) δ: 178.7 (s, C = O), 178.0 (s, C = O), 155.1 (s, C-OH), 135.4(d), 133.6(d), 128.7(s), 127.8(d), 127.0(d), 126.5(s), 111.4(s) ppm. MS *m/z* (% rel. int.): 254 (98, *M*+2), 252 (100, *M*), 224(29, *M*-CO), 173(71, *M*-Br), 145 (30), 117(17), 105(66), 89(68), 77(42), 63(24), 50 (34).

2-Bromo-1,4-naphthoquinone (**4**). Yellow crystals from H_2O. M_r 237.0, m.p. 130 °C. Anal. $C_{10}H_5BrO_2$: C, H, Br. TLC, R_f values: 0.51(A), 0.64(B), 0.65(C), 0.82(D). UV λ_{max} in EtOH: 277–71 ($\varepsilon = 8000$), 252 ($\varepsilon = 12025$), 247 ($\varepsilon = 12125$) nm. IR ν_{max} (KBr disc): 3080, 1690, 1670 (C = O), 1600, 1580, 1300, 1255, 1065, 915, 830, 780, 700, 670 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 8.20–8.07 (m, 2H, H_8, H_5; lit.[8] 8.11, 8.03), 7.83–7.73 (m, 2H, H_6, H_7; lit.[8] 7.79, 7.78), 7.52(s, 1H, H_3; lit.[8] 7.55) ppm. ^{13}C NMR ($CDCl_3$) data are presented in Table 1. MS *m/z* (% rel. int.): 238(74, *M*+2), 236(76, *M*), 210(6), 208(6, *M*-CO), 158(11), 157(100, *M*-Br), 129(95), 104(26), 101(79), 76(51), 75(57), 53(13), 51(22), 50(22).

Brominated 1-(1-naphthoxy)-2,3-propylene glycol (**5**). Slightly grey crystals from EtOH-H_2O. M_r 297.0, m.p. 113 °C. Anal. $C_{13}H_{13}BrO_3$: C, H. TLC, R_f values: 0(A), 0.03(B), 0.31(C), 0.48(D). UV λ_{max} in EtOH: 303–00 ($\varepsilon = 7750$), 237–36 ($\varepsilon = 23750$) nm. IR ν_{max} (KBr disc): 3340–20 (OH), 3080, 2940, 2860, 1596, 1460, 1428, 1378, 1265, 1240, 1130, 1040, 1022, 985, 885, 810, 767 cm^{-1}. MS *m/z* (% rel. int.): 298(30, *M*+2), 296(30, *M*), 224(99), 222(100), 195(7), 193(7), 143(13), 115(69), 57(11).

2,4-Dibromo-1-naphthol (**6**). Slightly grey crystals from EtOH-H_2O. M_r 301.9, m.p. 105 °C. Anal. $C_{10}H_6Br_2O$: C, H, Br, O. TLC R_f values: 0.61(A), 0.70(B), 0.73(C), 0.88(D). UV λ_{max} in EtOH: 289 ($\varepsilon = 7750$), 240–39 ($\varepsilon = 35250$), 218–17 ($\varepsilon = 32500$) nm. IR ν_{max} (KBr disc): 3420 (OH), 3080, 1588, 1450, 1376, 1330, 1235, 1210, 1145, 1060, 870, 835, 760, 670, 645 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 8.25–8.09 (m, 2H; lit.[12] 8.25–8.14), 7.77 (s, 1H; lit.[12] 7.79), 7.65–7.50 (m, 2H; lit.[12] 7.60), 5.93 (s, 1H, OH) ppm. ^{13}C NMR ($CDCl_3$) data are presented in Table 1. MS *m/z* (% rel. int.): 304(47, *M*+4), 302(100, *M*+2), 300(52, *M*), 195(31), 193(33), 142(13), 113(66), 97(19), 87(15); 74(8), 63(23).

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