The Structure of Bis(aminomethylated) Toluhydroquinones

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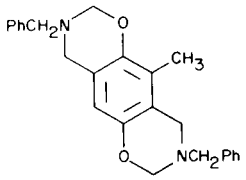
Two compounds made by the bisaminomethylation of toluhydroquinone have been reported in the literature. Both have been assigned incorrect structures. The first was prepared by Burke and Weatherbee (1) by the reaction of toluhydroquinone with benzylamine and formaldehyde in a molar ratio of 1:2:4. Structure **1** was assigned to it "based upon results obtained with methylamine, formaldehyde and hydroquinone." The second was prepared by the reaction of toluhydroquinone with formaldehyde and morpholine and reported in a recent patent (2). It was assigned structure **2**.



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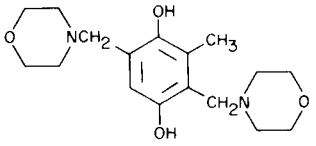
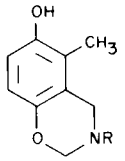


2

It is the purpose of this paper to present experimental evidence in support of new structural assignments for these products. The structure proofs are based upon arguments drawn from the reactions shown in Schemes I, II and III.

The monobenzoxazines of hydroquinone and its derivatives can be readily prepared in high yields (3). There are three structural isomers possible (**3**, **4** and **5**) for the monobenzoxazine obtained from toluhydroquinone. In practice, high yields of one isomer are produced (3).



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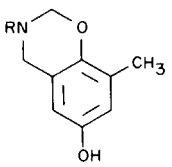

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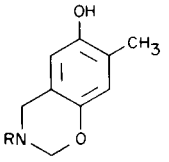

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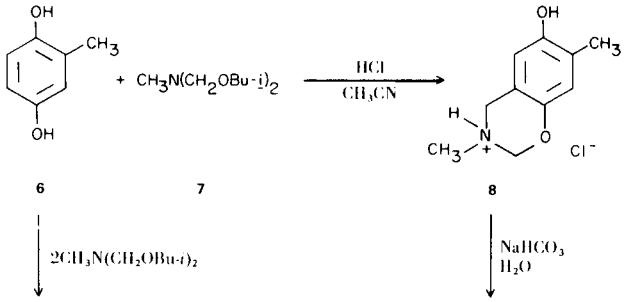
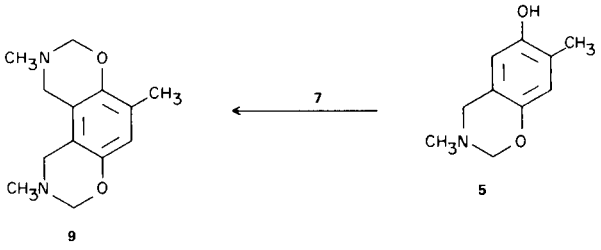
The 60-MHz nmr spectrum of the *N*-methyl monobenzoxazine shows two peaks (δ 6.25 and 6.30) in the aromatic region, which integrate for a total of two protons. At 90 MHz there is no obvious coupling of these protons as would be expected for compounds having structures **3** and **4**. Hence, the structure of the monooxazine prepared as in Scheme I from toluhydroquinone is established as that designated by **5**.

SCHEME I





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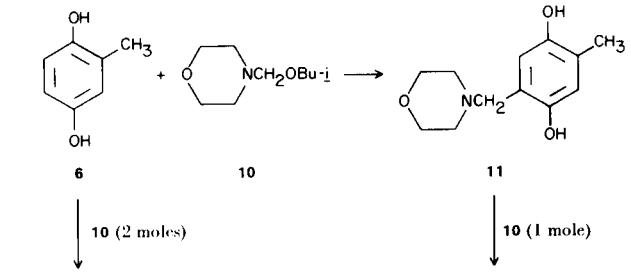
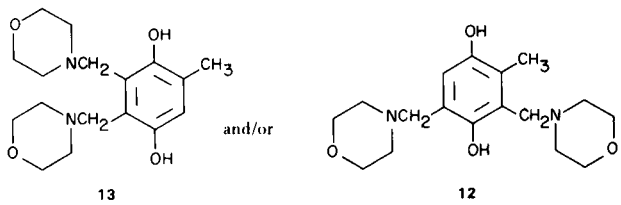
The conversion of the monooxazine **5** to the bisoxazine **9** is readily accomplished by the reaction of **5** with one molar part of bis(isobutoxymethyl)methylamine (**7**). Since the structure of **5** has been established, then the structure of the bisoxazine **9** must be as designated. The same compound (**9**) is obtained in a one-step process by the reaction of toluhydroquinone (**6**) with two molar parts of **7** (Scheme I).

SCHEME II



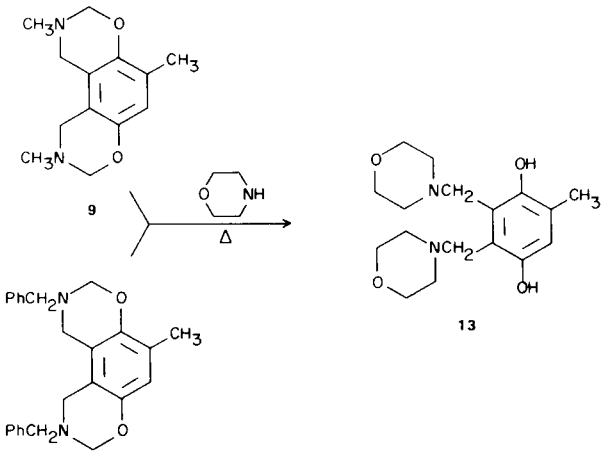


13 12

There are three possible isomeric structures for the bisaminomethylated compounds prepared by the reaction of toluhydroquinone with a secondary amine and formaldehyde or other aminomethylating agents such as **10**. The present discussion involves morpholine as the secondary amine and the possible structures are represented by **2**,

The bis(morpholinomethyl)toluhydroquinone described in the literature (2) (m.p. 157°) is the same compound that is obtained as the major product (m.p. 158-159°) according to the reactions shown in Scheme II. Determination of the correct structure is based upon a combination of the chemistry depicted in Schemes II and III.

SCHEME III



A mono(morpholinomethyl)toluhydroquinone is easily prepared by the reaction of equal molar quantities of **6** and **10**. Three isomeric structures may be envisioned. These are 2-methyl-3-morpholinomethyl-, 2-methyl-5-morpholinomethyl-, and 2-methyl-6-morpholinomethylhydroquinone. The absence of *ortho* or *meta* coupling with only two 1-proton singlets observed in the aromatic region of an nmr spectrum establishes the product to be the 2-methyl-5-morpholinomethyl derivative **11**.

When this mono-derivative **11** is converted to the bis compound by reaction with an equal molar part of **10**, one obtains the same bis(morpholinomethyl)toluhydroquinone (m.p. 158-159°) as that described in the literature (2). Compound **11** can yield bis compounds having only structures **12** and **13**. This rules out structure **2** and leaves one with the choice of **12** or **13**.

The isomeric bis(1,3-benzoxazines) of hydroquinone (4) have been shown to undergo an amine exchange reaction when refluxed with morpholine to yield the corresponding secondary morpholinomethyl derivatives (see Experimental section). When the bisoxazine **9** is refluxed in morpholine (Scheme III), one obtains a good conversion to the compound which is the major product (m.p. 158-159°) in Scheme II.

Since the structure of **9** has been established and since it can yield only 2-methyl-5,6-bis(morpholinomethyl)-hydroquinone, the structure of the product obtained must be as depicted by structure **13**.

During the preparation of 2-methyl-5,6-bis(morpholinomethyl)hydroquinone **13** in a one-step process by the reaction of toluhydroquinone with two molar parts of **10**, a small amount of a second isomer was isolated (m.p. 172°). The structure of this second isomer must have structure **2** or **12**. Based upon the assumption that the mono-morpholinomethyl derivative (**11**) is probably intermediate in its formation, it is designated as having structure **12**. These structural assignments have been based upon the chemistry of the *N*-methyl derivative **9**, whereas the bisoxazine reported in the literature, originally designated as **1**, is an *N*-benzyl derivative. In order to relate the established structure of the *N*-methyl derivative (**9**) to the *N*-benzyl derivative, the latter was prepared according to the original procedure (1) and refluxed with morpholine. It was converted in good yield to 2-methyl-5,6-bis(morpholinomethyl)hydroquinone **13** (Scheme III), thus indicating that it has structure **14**.

In summary, the compound which has been designated as **1** is in fact **14** and the bis(morpholinomethyl)hydroquinone previously assigned structure **2** is correctly designated as **13**.

EXPERIMENTAL

3,4-Dihydro-3,7-dimethyl-6-hydroxy-2*H*-1,3-benzoxazine Hydrochloride (8).

A solution of 8 g. of hydrogen chloride in 100 ml. of acetonitrile was cooled to −30°. To this was added a solution of 24.8 g. of toluhydroquinone (**6**) in 100 ml. of acetonitrile which had been cooled to −20°. Bis(isobutoxymethyl)methylamine (**7**) was then slowly added with stirring. The temperature was kept at $< 20°$ during the addition. The reaction mixture was left at room conditions. By the time the temperature had risen to 10° a crystalline product (**8**) was separating. After three hours it was collected by filtration and dried; 37.0 g. (85.8%), m.p. 190°. A sample recrystallized from acetonitrile or methanol melted at 192-193°.

Anal. Calcd. for $C_{10}H_{14}ClNO_2$: C, 55.6; H, 6.5; Cl, 16.5; N, 6.5. Found: C, 55.4; H, 6.2; Cl, 16.8; N, 6.5.

3,4-Dihydro-3,7-dimethyl-6-hydroxy-2*H*-1,3-benzoxazine (5).

The monooxazine hydrochloride **8** (21.5 g.) was dissolved in 250 ml. of water and stirred rapidly into a solution of 15 g. of sodium bicarbonate in 250 ml. of water. Crystalline free base **5** separated, 17.0 g. Recrystallization from ethanol yielded 11.5 g., m.p. 158°; nmr (DMSO-d_6) δ 2.02 (S, 3, 7-CH_3), 2.39 (S, 3, 3-CH_3), 3.66 (S, 2, $ArCH_2N$), 4.50 (S, 2, NCH_2O), 6.25 and 6.30 ppm (two S, 2, Ar–H).

Anal. Calcd. for $C_{10}H_{13}NO_2$: C, 67.0; H, 7.3; N, 7.8. Found: C, 66.8; H, 7.2; N, 8.0.

1,2,9,10-Tetrahydro-2,5,9-trimethyl-3*H*,8*H*-benzo[2,1-*e*:3,4-*e'*]bis-[1,3]oxazine (**9**).

One-Step Procedure.

A solution of 24.8 g. (0.2 mole) of toluhydroquinone (**6**) and 8.12 g. (0.4 mole) of bis(isobutoxymethyl)methylamine (**7**) in 100 ml. of benzene was refluxed for 5 hours. The solvent was removed under reduced pressure to yield 52.5 g. of crude product. Recrystallization from 50 ml. of ethanol gave 35.0 g. of bisoxazine **9**, m.p. 84-85°. A second recrystallization raised the m.p. to 88-89°; nmr (deuteriochloroform) δ 2.07 (S, 3, 5-CH_3), 2.50 (S, 6, 2-CH_3, 9-CH_3), 3.58 (S, 4, 1-CH_2, 10-CH_2–), 4.50, 4.53 (two S, 3-CH_2–, 8-CH_2–), 6.33 ppm (S, 1, 6-H).

Anal. Calcd. for $C_{13}H_{18}N_2O_2$: C, 66.6; H, 7.8; N, 12.0. Found: C, 66.9; H, 7.8; N, 12.2.

Two-Step Process.

A solution of monooxazine **5** (8.0 g., 0.045 mole) and 9.2 g. (0.045 mole) of bis(isobutoxymethyl)methylamine (**7**) in 50 ml. of benzene was refluxed for 2 hours. After removal of the solvent by a rotary evaporator the product crystallized. Two recrystallizations from ethanol yielded 6.0 g. of crystalline product, m.p. 88-89°. The nmr and ir spectra were identical with those of the product obtained from the one-step process.

2,9-Dibenzyl-5-methyl-1,2,9,10-tetrahydro-3*H*,8*H*-benz[2,1-*e*:3,4-*e'*]-bis[1,3]oxazine (**14**).

This compound was prepared by the method of Burke and Weatherbee (1), m.p. 104-105° (lit. m.p. 105°).

2-Methyl-5-morpholinomethylhydroquinone (**11**).

Toluhydroquinone (**6**) (24.8 g., 0.2 mole) was stirred with 34.6 g. (0.2 mole) of 4-isobutoxymethylmorpholine (**10**). The temperature rose gradually to 47° and the reaction mixture became homogeneous. Benzene (50 ml.) was added and the solution heated just to its boiling point and then placed at room conditions for one hour. Benzene (70 ml.) and ligroin (b.p. 35-60°) (70 ml.) were added, and the product was allowed to crystallize. It was separated by filtration and recrystallized from 100 ml. of benzene to yield 27.5 g. (61.6%), m.p. 106-109°. An analytical sample recrystallized from 2-propanol melted at 114-115°; nmr (deuteriochloroform) δ 2.10 (S, 3, 5-CH_3), 2.33-2.56 (M, 4, $-CH_2-N-CH_2$), 3.44 (S, 2, $-CH_2N$), 3.50-3.75 (M, 4, $-CH_2OCH_2$), 6.20 (S, 1, Ar–H), 6.43 ppm (S, 1, Ar–H).

Anal. Calcd. for $C_{12}H_{17}NO_3$: C, 64.5; H, 7.6; N, 6.3. Found: C, 64.8; H, 7.8; N, 6.6.

2-Methyl-5,6-bis(morpholinomethyl)hydroquinone (**13**).

One-Step Process.

A solution containing 24.8 g. (0.2 mole) of toluhydroquinone (**6**) and 69.2 g. (0.4 mole) of 4-isobutoxymethylmorpholine (**10**) in 100 ml. of 2-propanol was refluxed for 7 hours and the solvent was then removed under vacuum at 50°. The partially crystalline syrup was dissolved in 200 ml. of ether and chilled. Compound **13** crystallized in a high state of purity; 16.5 g. (25.5%), m.p. 157°. Recrystallization from ethanol raised the m.p. to a constant value of 158-159°; nmr (deuteriochloroform) δ 2.09 (S, 3, 2-CH_3), 2.30-2.56 (M, 8, two $-CH_2\underset{|}{N}-CH_2$), 3.45-2.72 (M, 12, two $-CH_2-O-CH_2-$ and two $-CH_2-\underset{|}{N}-$), 6.39 ppm (S, 1, 2-H).

Anal. Calcd. for $C_{17}H_{26}N_2O_4$: C, 63.4; H, 8.1; N, 8.7. Found: C, 63.6; H, 8.1; N, 8.9.

A second crop, 3 g., was recrystallized from ethyl acetate to give 1.4 g., m.p. 171-172°. This isomer is tentatively designated as compound **12**, nmr (deuteriochloroform) δ 2.10 (S, 3, 2-CH_3), 2.36-2.61 (M, 8, two $-CH_2\underset{|}{N}-CH_2$), 3.46-3.75 (M, 12, two $-CH_2-O-CH_2-$ and two $CH_2\underset{|}{N}-$), 6.20 ppm (S, 1, 6-H).

Anal. Calcd. for $C_{17}H_{26}N_2O_4$: C, 63.4; H, 8.1; N, 8.7. Found: C, 63.4; H, 8.0; N, 9.0.

Two-Step Process.

The monoaminomethylated compound **11** (22.3 g., 0.1 mole) was refluxed for 16 hours in 100 ml. of 2-propanol with 17.3 g. (0.1 mole) of 4-isobutoxymethylmorpholine. The crystalline product, 10.0 g., m.p. 158-159°, which separated upon cooling had nmr and ir spectra identical with those of compound **13** prepared by the one-step method. Another 4 g. of **13** was obtained from the filtrate. The remainder of the product was a mixture of **13** plus either the 3,5-isomer **12**, or the mono-derivative **11**. Thin layer chromatography and nmr cannot distinguish between **11** and **12** when they are mixed with **13**.

Conversion of 1,2,8,10-Tetrahydro-2,5,9-trimethyl-3*H*,8*H*-benzo-[2,1-*e*:3,4-*e'*]bis[1,3]oxazine (**9**) to 2-Methyl-5,6-bis(morpholinomethyl)hydroquinone (**13**).

The bisoxazine (**9**) (9.36 g., 0.04 mole) was heated at reflux temperature in 100 ml. of morpholine for 7 hours. The morpholine was removed under vacuum at 50°. The product was dissolved in 50 ml. of warm 2-propanol and cooled. The crystalline product obtained, 10.0 g. (77.6%), m.p. 155-158°, had nmr and ir spectra identical with those of the compound prepared directly from **6** or by the interchange reaction of **14** with morpholine.

Conversion of 2,9-Dibenzyl-5-methyl-1,2,9,10-tetrahydro-3*H*,8*H*-benz[2,1-*e*:3,4-*e'*]bis[1,3]oxazine (**14**) to 2-Methyl-5,6-bis(morpholinomethyl)hydroquinone (**13**).

The bisoxazine **14** (7.72 g., 0.02 mole) was heated at reflux in 50 ml. of morpholine for 7 hours. The morpholine was removed at 50° under vacuum. Compound **13** crystallized. Fifty ml. of 2-propanol was added and the mixture chilled in ice water. Upon filtration 3.3 g. (51.2%), m.p. 157-159° was obtained. This compound had identical nmr and ir spectra with those of the product prepared from toluhydroquinone and 4-isobutoxymethylmorpholine as described above.

Conversion of 3,7-Dimethyl-2,3,4,6,7,8-hexahydro-1,5-dioxa-3,7-diazaanthrazene to 2,5-Bis(morpholinomethyl)hydroquinone.

A solution of the bisoxazine (4) (11.0 g., 0.05 mole) was heated at reflux for 5 hours in 60.0 g. of morpholine. The morpholine was removed at 50° under vacuum during which time 2,5-bis-(morpholinomethyl)hydroquinone crystallized. It was triturated in a mixture of ether and ligroin, filtered, washed with ether and dried; yield, 9.35 g. (60.7%), m.p. 197-200° (lit. (5) 201-203°). A sample recrystallized from 2-propanol melted at 201-203°. The nmr spectrum was in accord with the structure.

Conversion of 3,6-Dimethyl-2,3,4,5,6,7-hexahydro-1,8-dioxa-3,6-diazaphenanthrene to 2,3-Bis(morpholinomethyl)hydroquinone.

A solution of bisoxazine (4) (11.0 g., 0.05 mole) was allowed to react with morpholine (60.0 g.) in the same manner as described above. The isolation was similar. The first crop of 2,3-bis(morpholinomethyl)hydroquinone (12.5 g., 81.1%) melted at 181-183°, (lit. (6), 185-186°). A sample recrystallized from 2-propanol melted at 183-185°. The nmr spectrum was in accord with the structure.

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