Russian Journal of Organic Chemistry, Vol. 39, No. 1, 2003, pp. 92–95. Translated from Zhurnal Organicheskoi Khimii, Vol. 39, No. 1, 2003, pp. 101–104.

^{1}H NMR Study of Quaternization of 2,4-Di-*tert*-butyl-6-dimethylaminomethylphenol

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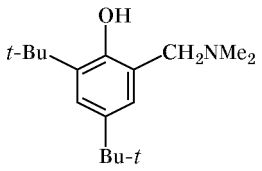
Received January 16, 2002

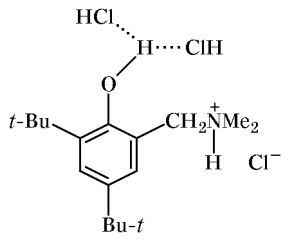
Abstract—The possibility was revealed for exhaustive protonation of 2,4-di-*tert*-butyl-6-dimethylaminomethylphenol with participation of lone electron pairs on both nitrogen and oxygen atoms. The reaction of the title compound with alkyl halides includes concurrent and consecutive processes leading to formation of the corresponding hydrohalides and quaternization products. The latter undergo spontaneous oxidation with atmospheric oxygen to give quaternary 6,8-di-*tert*-butyl-3-methyl-2*H*-3,4-dihydro-1,3-benzoxazine derivatives which were detected by ^{1}H NMR spectroscopy.

An essential element of the *o*-dialkylaminomethylphenol structure is the presence of H-chelate ring involving the hydroxy proton and nitrogen atom of the *ortho*-substituent. The strength of such intramolecular hydrogen bond depends on the nature of substituents on the nitrogen and in position *6* of the ring, and it varies over a wide range. This follows from the position of the OH signal in the ^{1}H NMR spectra, which appears in the δ range from 8 to 12 ppm ($CDCl_3$) [1], depending on the substrate structure, as well as from specific behavior of such compounds in reactions with acids and alkyl halides [2].



I

The present communication reports on the results of our ^{1}H NMR study of the reactions of 2,4-di-*tert*-butyl-6-dimethylaminomethylphenol (**I**) with hydrogen halides HX (X = Cl, Br) and alkyl halides (MeI, PrBr, $C_9H_{19}Br$, $C_{16}H_{33}Br$) in various solvents (acetone, DMSO, $CDCl_3$). In the ^{1}H NMR spectrum of phenol **I** in $CDCl_3$, the chelated OH proton gives a broadened signal at δ 11.3 ppm, which suggests formation of a strong intramolecular hydrogen bond. The reaction of **I** with excess concentrated hydrochloric acid leads to protonation of both hydroxy and amino group. Stoichiometric parameters of the process change with time: In the initial period we observed formation of salt **III** whose ^{1}H NMR spectrum is given in table.



II

The signal from the $\overset{+}{N}H$ proton almost does not change its position on raising the temperature, while the O**H**·2HCl signal shows a strong temperature dependence (δ 3.8 ppm at 50°C, 3H, diffuse signal due to exchange). This may be explained by protonation of both electron pairs on the oxygen atom or by the presence of a specific "stoichiometric" coordination sphere around the hydroxy group. On prolonged storage, the spectrum of the mixture is transformed into that corresponding to aminophenol **I** hydrochloride (salt **IIIa**), presumably as a result of phase separation in the system $CDCl_3$–HCl–H_2O and decomposition of the OH coordination sphere. Salt **IIIa** precipitates on removal of the solvent.

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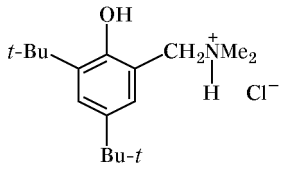
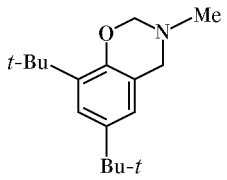
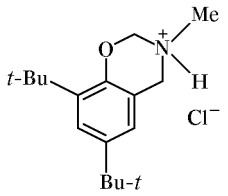


IIIa

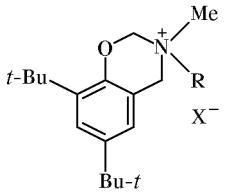
Aminophenol **I** was subjected to quaternization with alkyl halides RX both on a preparative scale and in an NMR ampule using $CDCl_3$ and $(CD_3)_2CO$ as solvents. The formation of quaternary ammonium salts in $CDCl_3$ was very slow; the process was much faster in $(CD_3)_2CO$, presumably due to weakening of the intramolecular hydrogen bond. The reaction gave two- or three-component mixtures of products which consisted of hydrohalides **III** and alkylation products of the initial aminophenol and its heterocyclic derivative, 6,8-di-*tert*-butyl-3-methyl-2*H*-3,4-dihydro-1,3-benzoxazine (**IV**). With the goal of identifying the products and assigning their ^{1}H NMR signals we synthesized some model compounds: hydrohalides **IIIa**–**IIIc**, benzoxazine **IV**, its hydrochloride **V**, and quaternary salts **VIa**–**VId**.



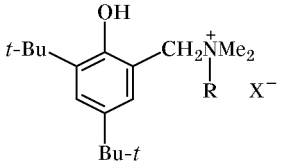
IV



V



VIa–**VId**

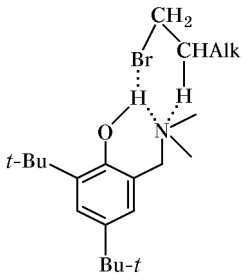


VIIa–**VIId**

VI, **VII**, X = I, R = Me (**a**); X = Br, R = Pr (**b**), C_9H_{19} (**c**), $C_{16}H_{33}$ (**d**).

According to the ^{1}H NMR data, the reaction of phenol **I** with methyl iodide in anhydrous acetone gave a mixture of salts which precipitated from the reaction mixture. The mixture contained quaternary derivatives of initial phenol **I** and oxazine **IV**, compounds **VIIa** and **VIa**, respectively. The concentration of salt **VIIa** decreases with time, and salt **VI** becomes the predominant product. Presumably, the former is the primary alkylation product, and it undergoes oxidative cyclization to benzoxazinium salt **VIa** on exposure to air. On prolonged storage of the reaction mixture, signals belonging to hydroiodide **IIIc** appear in the ^{1}H NMR spectrum. Taking into account that the initial methyl iodide contained no free hydrogen iodide (^{1}H NMR data), the formation of salt **IIIc** may be explained by solvolysis of methyl iodide with traces of water present in the solvent. Direct dehydroiodination of MeI by the action of aminophenol **I** seems to be also possible but less probable. An analogous pattern was observed in the alkylation of **I** with propyl bromide, nonyl bromide, and hexadecyl bromide with the difference that in the initial period almost simultaneous formation of two aminophenol salts, hydrobromide **IIIb** and **VIIb**–**VIId** occurred. The corresponding benzoxazine derivatives **VIb**–**VId** accumulated in the reaction mixture as a result of further oxidation of **VII**. Compounds **VIb**–**VId** characteristically show in the ^{1}H NMR spectra nonequivalence of signals from protons of both methylene groups in the heterocyclic moiety: the geminal coupling constants ^2J are similar for all R). The structure of salts **VI** implies the possibility for donor–acceptor interaction between the heteroatoms. Presumably, an analogous interaction leading to formation of intramolecular charge-transfer complex is also possible for "open" quaternary salts **VII**. As a result, they acquire partial diradical properties which facilitate their reaction with atmospheric oxygen. This assumption is consistent with the stability of initial aminophenol **I** in solution and ready oxidation of salts **VII**.

Thus the reaction of aminophenol **I** with RBr is a series of concurrent and consecutive processes, including direct alkylation with subsequent oxidation of the resulting quaternary salt and dehydrobromination of RBr by the action of initial aminophenol **I**. An important factor for the latter process may be coordination of the hydroxy proton in **I** with bromine atom of alkyl bromide, which gives rise to a cyclic transition state favorable for elimination of hydrogen bromide.



Participation of atmospheric oxygen in the formation of oxazine derivatives during quaternization of aminophenol **I** was confirmed by special experiment.

^{1}H NMR spectra of compounds **I**–**VII**

Compound no.	Solvent	Chemical shifts δ, ppm
I	$CDCl_3$	1.28 s (9H, *t*-Bu); 1.41 s (9H, *t*-Bu); 2.31 s [6H, $N(CH_3)_2$]; 3.60 s (2H, CH_2N); 6.81 d (1H, Ar); 7.21 d (1H, Ar); 11.30 s (1H, OH)
II	$CDCl_3$, Excess HCl–H_2O	1.30 s (9H, *t*-Bu); 1.44 s (9H, *t*-Bu); 2.87 d [6H, $N(CH_3)_2$]; 4.21 d (2H, CH_2N); 5.75 s, 5,86 s, and 5.96 s (3H, OH·2HCl); 7.05 d (1H, Ar); 7.44 d (1H, Ar); 10,67 m [1H, NH^+, J(NH, CH_3) = 3.8 Hz; J(NH, CH_2) = 4.7 Hz]
IIIa	$CDCl_3$	1.29 s (9H, *t*-Bu); 1.43 s (9H, *t*-Bu); 2.88 br [6H, $N(CH_3)_2$]; 4.22 br. (2H, $ArCH_2N$); 6.35 s (1H, OH); 7.06 d (1H, Ar); 7.44 d (1H, Ar); 10.60 br (1H, NH^+)
IIIb	$CDCl_3$	1.30 s (9H, *t*-Bu); 1.45 s (9H, *t*-Bu); 2.86 d [6H, $N(CH_3)_2$]
IV	$CDCl_3$	1.34 s (9H, *t*-Bu); 1.44 s (9H, *t*-Bu); 2.64 s (3H, NCH_3); 4.0 s (2H, CH_2N); 4.81 s (2H, OCH_2); 6.85 d (1H, Ar); 7.21 d (1H, Ar)
V	$CDCl_3$, Excess HCl–H_2O	1.28 s (9H, *t*-Bu); 1.37 s (9H, *t*-Bu); 3.13 br (3H, NCH_3); 4.27 d (1H, $ArCH_2N$); 4.97 d (1H, $ArCH_2N$, ^2J = 5.35 Hz); 5.18 br (2H, OCH_2N); 6.99 d (1H, Ar); 7.28 d (1H, Ar); ~7.0 (NH·HCl, exchangeable)
VIa	$CDCl_3$	1.28 s (9H, *t*-Bu); 1.37 s (9H, *t*-Bu); 3.68 s [6H, $\overset{+}{N}(CH_3)_2$]; 4.96 s (2H, CH_2N^+); 5.39 s (2H, OCH_2); 6.94 d (1H, Ar); 7.34 d (1H, Ar)
VIb	$CDCl_3$	1.08 t (3H, $CH_3CH_2CH_2N$); 1.27 s (9H, *t*-Bu); 1.36 s (9H, *t*-Bu); 1.97 m (2H, CH_3CH_2-CH_2N); 3.85 t (2H, $CH_3CH_2CH_2N$); 4.97 d (1H, $ArCH_2N$); 5.09 d (1H, $ArCH_2N$, ^2J = 15.35 Hz);5.51 d (1H, OCH_2N); 5.62 d (1H, OCH_2N, ^2J = 8.40 Hz)
VIc	$CDCl_3$	0.87 t [3H, $CH_3(CH_2)_7CH_2N^+$]; 1.28 s (9H, *t*-Bu); 1.36 s (9H, *t*-Bu); 1.25 m [14H, $CH_3(CH_2)_7CH_2N^+$]; 3.62 s (3H, $\overset{+}{N}CH_3$); 3.82 t [2H, $CH_3(CH_2)_7CH_2N^+$]; 4.94 d (1H, $ArCH_2N^+$); 5.10 d (1H, $ArCH_2N$, ^2J = 15.35 Hz); 5.44 d (1H, OCH_2), 5.62 d (1H, OCH_2, ^2J = 8.40 Hz); 6.93 d (1H, Ar); 7.32 d (1H, Ar)
VIIa	$CDCl_3$	1.30 s (9H, *t*-Bu); 1.44 s (9H, *t*-Bu); 3.00 s [9H, $\overset{+}{N}(CH_3)_3$]; 5.20 s (2H, $ArCH_2N^+$); 7.01 (8.64) s (1H, OH); 7.19 d (1H, Ar); 7.44 d (1H, Ar)
VIIc	$CDCl_3$	0.87 t [3H, $CH_3(CH_2)_8N^+$]; 1.25 m [2H, $CH_3CH_2(CH_2)_7$]; 1.28 s (9H, *t*-Bu); 1.43 s (9H, *t*-Bu); 1.86 m (2H, NCH_2CH_2Alk); 2.98 s [6H, $N(CH_3)_2$]; 3.82 t [2H, $\overset{+}{N}CH_2(CH_2)_7$-$CH_3$]; 5.21 s (2H, $ArCH_2N^+$); 7.04 d (1H, Ar); 7.46 d (1H, Ar); 7.58 s (1H, OH)

When the reaction of aminophenol **I** with methyl iodide in acetone was carried out in a degassed system, the only alkylation product was salt **VIIa** (according to the ^{1}H NMR data).

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker WH-250 spectrometer at 250 MHz. The reaction mixtures were analyzed by TLC using Silufol UV-254 plates. Alkyl halides were of chemically pure grade; According to the ^{1}H NMR data, they contained no free hydrogen halide. Phenol **I** and oxazine **IV** were synthesized by the procedure described in [3].

2,4-Di-*tert*-butyl-6-dimethylaminomethylphenol hydrochloride (IIIa) and hydrobromide (IIIb). Gaseous hydrogen chloride was passed through a solution of 0.26 g (1 mmol) of phenol **I** in dry diethyl ether. Hydrobromide **IIIb** was obtained by adding concentrated hydrobromic acid in a dropwise manner to a solution of phenol **I** in anhydrous acetone. The precipitate was filtered off, washed with diethyl ether and hexane, and dried under reduced pressure. **IIIa**: yield 0.27 g (91%), mp 230–231°C (sublimes); **IIIb**: yield 0.3 g (89%), mp 246–247°C.

6,8-Di-*tert*-butyl-3-methyl-2,4-dihydro-2*H*-1,3-benzoxazine hydrochloride (V) and benzoxazinium salts VIa–**VId** were synthesized in NMR ampules by adding concentrated hydrochloric acid or alkyl halide (MeI, PrBr, C_9H_9Br, or $C_{16}H_{33}Br$) to a solution of benzoxazine **IV** in acetone-d_6.

The reactions of aminophenol I with alkyl halides were carried out in anhydrous acetone, the reactant ratio 1 : RX being 1 : 1.5. The mixture was

kept for 3–5 days, and the colorless precipitate was filtered off, washed with hexane, dried under reduced pressure, and analyzed by ^{1}H NMR spectroscopy using $CDCl_3$ or DMSO-d_6 as solvent.

a. RX = MeI. Crystalline product, mp 262–263°C; The ^{1}H NMR spectrum in $CDCl_3$ corresponds to a mixture of salts **VIa** and **VIIa** at a ratio of ~1:4 with a small impurity of hydroiodide **IIIc**.

b. RX = PrBr. Crystalline product, mp 225–226°C; a three-component mixture of hydrobromide **IIIb** and salts **VIb** and **VIIb** at a ratio of ~5:1:4 (^{1}H NMR data). As described above for the reaction with MeI, the fraction of benzoxazinium salt **VIb** increases with time, and the amount of salt **VIIb** decreases.

c. RX = $C_9H_{19}Br$ and $C_{16}H_{33}Br$. As in the reaction with PrBr, three-component product mixtures were obtained, which contained ~50% of hydrobromide **IIIb**; the ratio of salts **VIc** and **VIIc** (**VId** and **VIId**) changed with time toward increased fraction of **VI**.

Reaction of phenol I with methyl iodide in the absence of oxygen. A solution of aminophenol **I** and a small excess of methyl iodide in anhydrous acetone was placed in an ampule, and the ampule was cooled with liquid nitrogen, evacuated to 10^{-2} mm, defreezed, freezed and evacuated again, sealed, and kept for 3 days at room temperature. The ampule was opened, and the crystalline product was washed and dried under reduced pressure. Its ^{1}H NMR spectrum in $CDCl_3$ coincided with the spectrum of salt **VIIa**; no benzoxazinium salt **VIa** was detected.

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