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# α-Amino acid-assisted autoxidation of naphthalene proton sponge affording 1,4-naphthoquinone nitrogen derivatives

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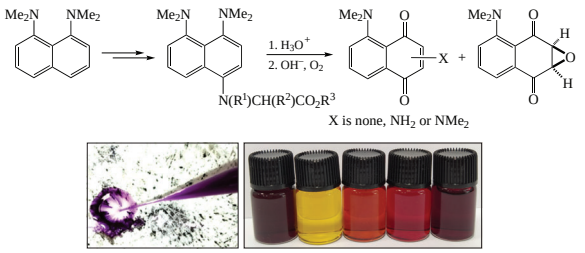
**1,8-Bis(dimethylamino)naphthalene (naphthalene proton sponge) equipped at position 4 with N-terminal α-amino acid residues undergoes unprecedented easy autoxidation in basic medium forming 5-dimethylamino-1,4-naphthoquinone along with minor amounts of its derivatives. The new reaction is of interest against the background of wide distribution of 1,4-naphthoquinones in nature, their high biological significance and extremely limited information on nitrogen compounds of this series.**

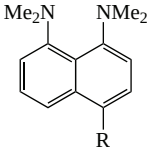



*Keywords*: proton sponge, amino acids, 1,4-naphthoquinone, hydrolysis, autoxidation.

*The authors dedicate this article to the outstanding scientist Academician I. P. Beletskaya, who paved the way for Russian science into many new areas of organic and physical organic chemistry, from carbanions to cross-coupling reactions catalyzed by transition metals.*

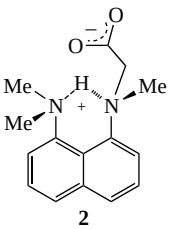
1,4-Naphthoquinones, as well as quinones in general,[1,2] are widely distributed in the plant and animal kingdom showing a striking variety of biochemically significant properties.[3,4] As one of the key natural redox systems, quinones are involved in dozens of electron transfer processes including the respiratory chain and photosynthesis. Simple derivatives of 1,4-naphthoquinone constitute an extensive group of vitamins K.[5] Vegetative 2-hydroxynaphthoquinone (lawsone) and 5-hydroxynaphthoquinone (juglone) show allelopathic effects.[6] Quinones are considered as an important type of pharmacophores.[7,8] Due to their bright and stable colour, quinones have long been used to dye wool, silk, and leather.[9]

Considering a great natural abundance of nitrogen compounds, it is surprising that most natural quinones lack nitrogen functionalities. In this communication, we report our discovery of a reaction that opens an unexpected and relatively uncomplicated route to 5-dialkylamino-1,4-naphthoquinones and their derivatives. Its essence lies in the alkaline autoxidation of 1,8-bis(dimethylamino)naphthalene (DMAN, **1a**) containing 4-positioned amino acid moieties, the starting reactants having been triamines **1b**,**c**. Previously, we described the first representatives of unnatural DMAN-based α-amino acids[10] when the amino acid residue was linked by its N-termini to 8-dimethylamino-1-naphthyl moiety and existed as zwitterion **2** with the chelated proton preferably resided on the adjacent $NMe_2$ group.



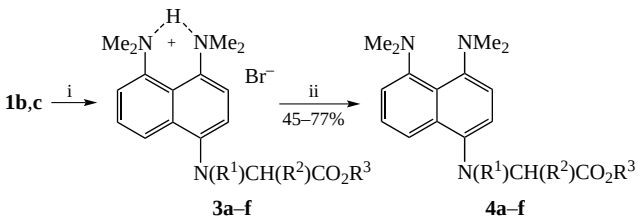

**1a–d**

**a** R = H
**b** R = $NH_2$
**c** R = NHMe
**d** R = $NMe_2$



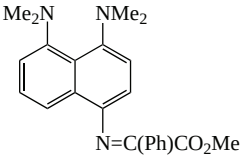

**2**

The initial motive of this work was the synthesis and study of compounds isomeric to **2**, in which the DMAN residue would be attached to an amino acid through position 4. To achieve this goal, we first treated earlier described[11] 4-amino and 4-methylamino DMANs **1b**,**c** with α-bromo acid esters (Scheme 1). The resulting crude salts **3a–f** were subjected to dehydrobromination with 10% aqueous KOH thus affording the desired amino acid esters **4a–f** in the form of bases in moderate




**3a–f** **4a–f**

**a** $R^1 = R^2 = H$, $R^3 = Me$
**b** $R^1 = R^2 = H$, $R^3 = Et$
**c** $R^1 = H$, $R^2 = R^3 = Me$
**d** $R^1 = H$, $R^2 = Me$, $R^3 = Et$
**e** $R^1 = R^3 = Me$, $R^2 = H$
**f** $R^1 = H$, $R^2 = Ph$, $R^3 = Me$

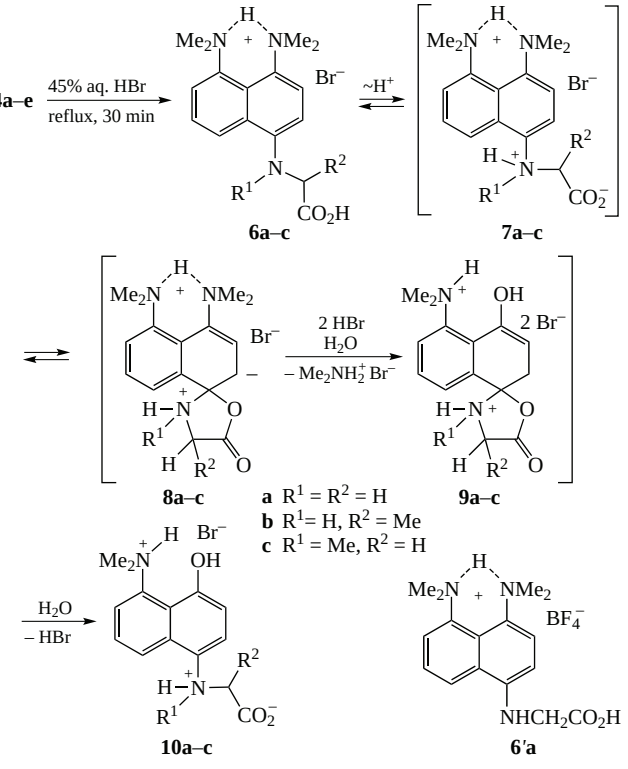



**5** (with **4f**)

**Scheme 1** *Reagents and conditions*: i, $BrCH(R^2)CO_2R^3$, MeCN, reflux, 72 h; ii, 10% aq. KOH.

to good yields. In the case of methyl phenylacetate derivative **4f**, a small amount (5%) of azomethine **5** was also obtained. The structures of thus obtained products were proved by spectral measurements, and for compounds **4c** and **5** the XRD studies were also performed (see Online Supplementary Materials, pp. S35–S36).

The target amino acids **6a–c** as slightly grayish hydrobromides were obtained in nearly quantitative yield by hydrolysis of esters **4a–e** with 45% aqueous HBr (Scheme 2). Although two circumstances complicated the work with salts **6a–c**, they turned out to be fortunate for elucidating the mechanism of subsequent transformations. The first complication was very poor solubility of salts **6a–c** in $CDCl_3$ and $CD_3CN$, so their NMR spectra could be recorded only in DMSO-$d_6$. The second point was the instability of salts **6a–c** in this medium possibly due to their pronounced hygroscopicity. Thus, in the proton spectra of even the freshly prepared solutions of glycine derivative **6a**, along with the expected peaks for $[NHN]^+$ ($\delta$ 18.4 ppm), OH (12.2 ppm), $CH_2$ (4.2 ppm), two different $NMe_2$ groups and five aromatic hydrogens ($\delta$ 7.8–8.3 ppm), the less shielded signals at $\delta$ 7.3–7.6 ppm of the second minor compound could be noticed. Its content grew rapidly and, judging by the disappearance of the peaks of the chelated $[NHN]^+$ proton and one of the $NMe_2$ groups, as well as the appearance of a characteristic triplet of the $[Me_2NH_2]^+$ cation at 7.1 ppm, it was identified as hydrobromide of 8-dimethylamino-1-naphthol derivative **10a** (see Online Supplementary Materials, p. S24). A similar hydrolytic substitution of the $NMe_2$ group was previously reported for two DMAN derivatives containing in position 4 such strong electron-withdrawing functionalities as $NO_2$[12] or pyridinium groups.[13] Evidently, the latter are necessary for the activation of 1-$NMe_2$ group to nucleophilic attack. The KOH/DMSO[12] system and water in dilute sulfuric acid[11] acted as the nucleophile in both these examples, and the process required many hours of boiling. As can be seen, such harsh conditions contrast sharply with the behavior of amino acids **6a–c**, which suggests a significant change in the substitution mechanism and, possibly, the presence of some kind of catalysis. We assume that, in our case, the activation of the 1-$NMe_2$ group is provided through the formation of equilibrium amounts of the zwitterionic amino acid intermediate **7a** while moisture penetrating the NMR ampoule due to the hygroscopicity of the mixture (or already present in DMSO-$d_6$) serves as nucleophile. Presumably, the carboxylate anion in **7a–c** as a nucleophile intramolecularly would attack position 4, which leads to oxazolinone spiro intermediates **8a–c**. In them, the 1-$NMe_2$ group becomes part of the enamine moiety and therefore should be easily hydrolyzed.[14] It is known[15] that oxazolines are prone to ring–chain tautomerism and rapidly equilibrate between open and closed forms. The ratio of the latter depends on their structure and conditions. It is logical to assume that secondary spiro intermediates **9a–c** should eventually aromatize into open form **10a–c**.




**Scheme 2**

The importance of hygroscopicity and medium polarity factors in the transformation **6** → **10** has been confirmed by the following experiment. We have prepared salt **6′a** (see Scheme 2) containing more hydrophobic $BF_4^-$ anion instead of $Br^-$. It turned out that tetrafluoroborate **6′a** dissolved well in $CD_3CN$ and, according to NMR data, remained stable for hours (see Online Supplementary Materials, p. S25). There were no changes even after adding a small amount of solid KOH to the ampoule. The gradual transformation of **6′a** into naphthoquinone **14** (see below) proceeded only upon its boiling in water and subsequent treatment with ammonia.

Further experiments with salts **6a–c** consisted in their deprotonation with the aim to obtain neutral amino acids or their carboxylates. When compounds **6a–c** were treated with an equimolar amount of 10% KOH solution, the initially colourless mixture turned dark bluish within minutes and the colour then rapidly deepened. Ultimately, a dark violet substance was isolated from the mixture, which turned out to be yet unknown 5-dimethylamino-1,4-naphthoquinone **14** (Scheme 3). Its structure was confirmed by XRD analysis (Figure 1),† which clarified that

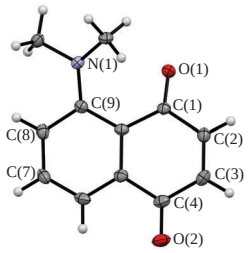


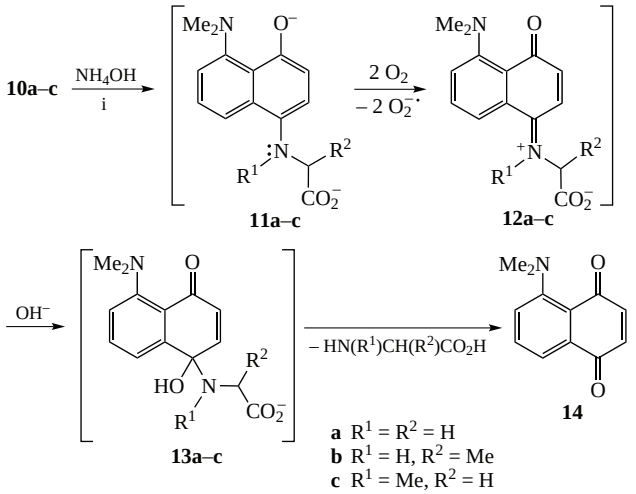

**Figure 1** Molecular structure and selected parameters of quinone **14**. Bond lengths and distances: N···O(1) (2.897 Å), C(1)=O (1.231 Å), C(4)=O (1.223 Å), N–C(8) (1.366 Å). Sum of CNC angles at nitrogen, Σ*N* (356.8°). Torsion angle C(2)–C(3)/C(7)–C(8) (7.9°). Deviation of atoms from the average naphthalene ring plane: O(1) (–0.458 Å), O(4) (+0.210 Å), N (+0.404 Å).

† *Crystal data for* **14**. $C_{12}H_{11}NO_2$ ($M$ = 201.22) monoclinic, space group *Pn* at 100(2) K, $a$ = 3.82850(10), $b$ = 9.6276(2) and $c$ = 12.8281(2) Å, $\beta$ = 92.367(2)°, $V$ = 472.431(17) Å$^3$, $Z$ = 2, $d_{calc}$ = 1.415 g cm$^{-3}$, $\mu$(CuK$\alpha$) = 0.790 mm$^{-1}$, $F$(000) = 212.0. Total of 12156 reflections were collected [1798 independent reflections with $I > 2\sigma(I)$, $R_{int}$ = 0.0355] and used in the refinement, which converged to $wR_2$ = 0.0708, GOOF = 1.039 for all independent reflections [$R_1$ = 0.0263 was calculated for 1798 reflections with $I > 2\sigma(I)$].

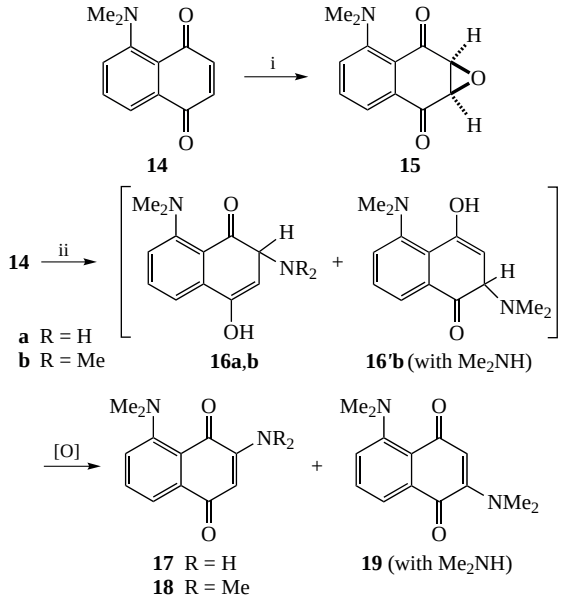
X-ray diffraction data were collected on an XtaLAB Synergy, HyPix diffractometer equipped with a Hybrid Pixel Array Detector (mirror monochromator, ω-scanning, CuKα radiation, 1.54184 Å). Using Olex2,[16] the structure was solved with the ShelXT[17] structure solution program using Intrinsic Phasing and refined with the ShelXL[18] refinement package using Least Squares minimization.

Online Supplementary Materials present crystallographic data for compounds **4c**, **5**, **14**·$HBF_4$, **15**, **17**, **18** and **19**.

CCDC 2184190–2184197 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk.




**Scheme 3** *Reagents and conditions*: i, $NH_4OH$ (aq.), room temperature, 2 h.




**Scheme 4** *Reagents and conditions*: i, $H_2O_2$ (aq.), 30 °C, 2 h; ii, $R_2NH$ (aq.) (R = Me or H), room temperature, contact with air, 1 h.

the deep colour of **14** was due to the effective conjugation of the almost planar $NMe_2$ group ($\sum N = 356.8°$) with the C(4)=O carbonyl (see Online Supplementary Materials, p. S16).

We believe that the formation of quinone **14** starts with the generation of naphthol derivatives **10a–c** (see Schemes 2, 3) and their dianions **11a–c**, which undergo rather fast autoxidation (see Online Supplementary Materials, p. S43). Autoxidation is indicated by such signs as the appearance of hydrogen peroxide in the reaction mixture (see below), a quite rapid development of colour in the upper layer of the solutions of **6a–c** even in the NMR ampoule (see Online Supplementary Materials, Figure S3), as well as an instantaneous and not disappearing for many days staining of experimenter's fingers in case of accidental contact with the reaction mixture. The autoxidation results in the formation of quinone iminium intermediates **12a–c** followed by hydrolytic elimination of α-amino acid residue (**12** → **13** → **14**, see Scheme 3). Alternatively, the transition **12** → **14** could be accompanied by decarboxylation of intermediates **12** or **13**, as occurred in the biochemical decarboxylation of α-amino acids.[19] This process is usually preceded *via* preliminary conversion of the α-amino group to the azomethine functionality (*cf*. also the recently proposed method for the industrial processing of protein waste[20]). It is noteworthy that although in our case the α-$NH_2$ group is also converted to iminium intermediate **12**, the amino acid residue is eliminated as such without decarboxylation. This was proven by HRMS examination of the reaction mixture formed during the oxidation of the alanine-containing compound **10b** (see Online Supplementary Materials, p. S46). In addition, in the case of at least partial decarboxylation of compound **12b**, the mixture should contain (by analogy with the formation of amines **17**–**19**, Scheme 4) the addition product of ethylamine to quinone **14**. However, no trace of it was found.

To optimize the yield of **14**, most of our experiments were carried out with aqueous ammonia (instead of KOH solution) and on aeration of suspension of compounds **6a–c** by periodically stirring them in an evaporating dish. It was found that under ambient conditions the reaction was completed in about 2 h and the maximum yield of quinone **14** reached 58%. An increase in the yield is limited by partial tarring of the reaction mixture and further transformations of compound **14**, which reacts with ammonia, dimethylamine, and hydrogen peroxide (see Scheme 4). We were able to isolate four such side-products: epoxide **15** and amines **17**–**19** (Table 1). Their structure was confirmed by spectral and XRD measurements (see Online Supplementary Materials, pp. S37–S42). Amusingly, the formation of amines **18** and **19** looks like the wandering behavior of the $NMe_2$ group, which has lost its original place in the DMAN residue. All the mentioned side products were also prepared independently from quinone **14** (see Online Supplementary Materials, p. S12), but its reactivity will be described in more detail in a separate communication.

**Table 1** Results of experiments on alkaline autoxidation of compounds **4a–e**.

| Entry | Starting compound | Product yield (%) | | | | |
|---|---|---|---|---|---|---|
| | | **14** | **15** | **17** | **18** | **19** |
| 1 | **4a** | 45 | 3.5 | 3 | 1 | 8 |
| 2 | **4b** | 58 | 4 | 2 | 3 | 6 |
| 3 | **4c** | 45 | 2 | 2 | 2.6 | 6 |
| 4 | **4d** | 41 | 3 | 3 | 1 | 12 |
| 5 | **4e** | 49 | 5 | 7 | 1 | 6 |

In conclusion, it should be emphasized that the specificity of α-amino acids attached to position 4 of DMAN is remarkable sice they activate the autoxidation of the naphthalene ring both through the N- and C-termini. Empirically, the process proceeds slightly easier for the alanine compound, followed by the *N*-methylglycine and glycine derivatives. In the case of DMAN with a 2-phenylglycine substituent, oxidation is accompanied by the formation of a complex mixture of difficult-to-identify substances and significant tarring. The reaction does not proceed for similar amino acid derivatives of aniline and 1-amino-naphthalene, which indicates the important role of the proton sponge nature of the substrates (see Online Supplementary Materials, pp. S12–S15). It is important to note that refluxing amines **1b**,**d** for many hours in 45% HBr leads to only partial substitution of one of the $NMe_2$ groups by OH (see Online Supplementary Materials, p. S34), which after subsequent treatment of the mixture with aqueous ammonia is also able to form compound **14**. These experiments show that the introduction of amino acid residue into position 4 of DMAN makes the formation of quinone **14** dramatically easy. On the whole, the reaction herein discovered can be considered as a new example of the manifestation of organocatalytic properties by amino acids (see review[21]).

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at the Southern Federal University). We also thank Dr. Anna V. Tkachuk (Scientific and Educational Laboratory of Resonance Spectroscopy, Department of Natural and High Molecular Compounds Chemistry, Southern Federal University) for routine NMR measurements and Research Park of St. Petersburg State University for selected XRD and NMR studies.

*Online Supplementary Materials*

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.02.015.

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