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Nitration versus Nitrosation Chemistry of Menthofuran: Remarkable Fragmentation and Dimerization Pathways and Expeditious Entry into Dehydromenthofurolactone

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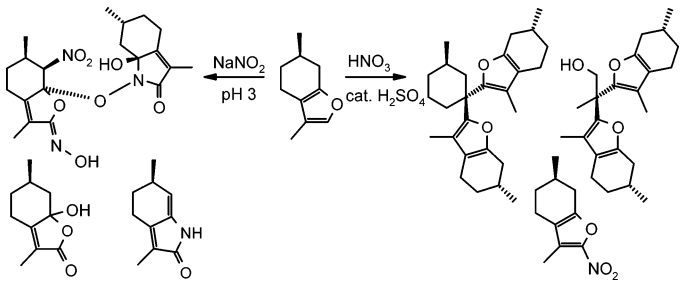

The reaction chemistry of menthofuran (**1**), a toxic furan terpenoid from various mint oils, with nitric acid and nitrous acid has been investigated. Treatment of **1** with nitric acid afforded a 1:1 mixture of the bisfuran derivatives **5** and **6**, resulting from the unexpected cleavage of the furan into two carbonyl fragments (3-methylcyclohexanone and hydroxyacetone) and their subsequent trapping by unreacted **1**. Under conditions of high dilution, the nitrofuran derivative **7** was formed instead as the major reaction product. During investigation of this chemistry, it was found that oxidation of **1** with DDQ led to the important fragrant monoterpenoid **4** [dehydromenthofurolactone (anhydro Woodward−Eastman lactone)] in 44% yield. Exposure of **1** to nitrite ions at pH 3 afforded a completely different type of products, encompassing the known lactone **14**, the lactam **15**, and the remarkable dimer **16**, bearing a *N*-hydroxy-2-pyrrolinone moiety linked to a nitrooximinofuran unit by an oxygen bridge. By using a combined spectroscopic and DFT approach, the constitution and configuration of **16** could be determined. These results fill a gap in the chemistry of furan compounds and describe routes to menthofuran-derived scaffolds of potential synthetic and biomedical relevance.

Introduction

(*R*)-Menthofuran (**1**), a minor terpenoid of peppermint (*Mentha piperita* L.), is better known as a mammalian metabolite and the proximate toxin of pulegone (**2**), the major constituent of pennyroyal oil.[1] This popular fragrance is also a potent hepatotoxin and is obtained from *Mentha pulegium* L., a plant used in folk medicine as an abortifacient.[2] The metabolic

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(1) Khojasteh-Bakht, S. C.; Koenigs, L. L.; Peter, R. M.; Trager, W. F.; Nelson, S. D. *Drug Metab. Dispos.* **1998**, *26*, 701−704.
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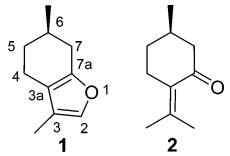
conversion of **2** to **1** underlies the poisonous properties of pennyroyal oil.[1] Thus, oxidation of the allylic methyl of **2** triggers a cyclodehydration to **1**, eventually converted into a reactive epoxide that acts as an ultimate carcinogen because of its marked electrophilic properties.[1,3]

Due to its unfavorable safety profile and bitter taste, **1** is an undesirable constituent of peppermint oil. On the other hand, **1** is also the precursor of menthofurolactone (**3**) and dehydromenthofurolactone (anhydro Woodward−Eastman lactone, **4**), two compounds whose sweet and persistent coumarinic odor is the hallmark of premium-quality peppermint oils.[4] Accordingly, considerable efforts have been devoted to elucidate the genetic and epigenetic factors that affect the formation of **1** in mint plants[5] and to develop chemical methods to remove it from peppermint oil while maintaining the sensory note of its oxidation products. These methods rely on the photosensitized oxygenation of the oil and its treatment with acids and have been recently complemented by the reaction with dimethyldioxirane.[6] An additional issue of interest is the reaction of **1** with nitric acid in the presence of catalytic sulfuric acid,[7] which forms the basis of a popular color test for peppermint oil. Despite the practical relevance of this reaction, little is known about the underlying chemistry, an unsurprising finding on account of the lack of information that currently exists on the chemistry of trisubstituted furans. These considerations prompted us to extend to menthofuran our studies on the behavior of bioactive natural products with nitrogenous mineral acids.[8]



1 **2** **3** **4**

Results and Discussion

The Reaction of 1 with Nitric Acid. Treatment of **1** with 40% nitric acid and catalytic sulfuric acid led to the instantaneous development of a purple color, while TLC analysis evidenced the complete conversion of **1** into two colorless, UV-absorbing compounds. Gravity column chromatography afforded the least polar compound as colorless crystals and the more polar reaction product as an amorphous white powder. The NMR spectra of the more polar product ($C_{23}H_{32}O_3$, HRMS) showed the presence of a pair of 2-menthofuranyl moieties and a three-carbon fragment. The two menthofuranyl moieties exhibited apparent chemical shift equivalence except for the signals of the pseudobenzylic methyl protons ($\Delta\delta = 0.02$ ppm) and carbon ($\Delta\delta = 0.04$) and the signal of C-3 ($\Delta\delta = 0.06$ ppm). The three-carbon fragment was identified as a 2-hydroxy-1-methylethylidene moiety by multiplicity considerations and by HMBC correlations between the methyl protons at δ 1.68 and the signals of the −CH< and $HOCH_2$ carbons (δ 44.3 and 69.2, respectively). Diagnostic HMBC correlations between the hydroxymethyl and the methyl protons of the three-carbon moiety (δ 3.94 and 1.68, respectively) and C-2 (δ 148.8) of the menthofuranyl residue eventually allowed identification of the compound as the bis(2-menthofuranyl) adduct of hydroxyacetone **5** (28% yield after crystallization).

The less polar compound ($C_{27}H_{38}O_2$, HRMS) resembled **5** in that NMR analysis showed the presence of two 2-menthofuranyl residues geminally bound to a seven-carbon moiety identified as a methylcyclohexane ring. Given the duplication of all the menthofuranyl protons, an extensive overlapping was present in the ^{1}H NMR spectrum, and the relative location of the substituents around the cyclohexane ring was not immediately apparent. However, the detection of six distinct ^{13}C NMR resonances for the cyclohexane core ruled out a symmetric 1,4-relationship between the two substituted carbons, while the lack of any detectable ROESY correlations between the methyl of the cyclohexane core (δ 0.82) and the furanyl methyls (δ 1.34 and 1.84) concurred to suggest a 1,3- rather than a 1,2-relationship between the substituted cyclohexane carbons. Accordingly, the product was formulated as 1,1-(bis-2-menthofuranyl)-3-methylcyclohexane (**6**) (39% yield after crystallization). These structures were supported by literature precedents for the formation of alkylidene−bisfuranyl structures from the reactions of furans with carbonyl compounds[9] and by the observation that, in the presence of catalytic amounts of strong acids, **1** reacted quickly with hydroxyacetone to afford a compound having ^{1}H and ^{13}C NMR spectra corresponding to those of **5** and with *rac*-3-methylcyclohexanone to afford the known **6**.[9b,10,11]

When the reaction of **1** with nitric acid was run under conditions of lower acidity (20% HNO_3, cat. H_2SO_4), the nitro derivative **7** was obtained as the major reaction product (18% yield), along with minor amounts of the adducts **5** and **6** (5 and 7%, respectively). Interestingly, formation of **5** and **6** did not occur with a variety of other mineral acids (H_2SO_4, HCl, H_3PO_4), while with 40% HNO_3 alone, the reaction was sluggish.

(3) Thomassen, D.; Knebel, N.; Slattery, J. T.; McClanahan, R. H.; Nelson, S. D. *Chem. Res. Toxicol.* **1992**, *5*, 123−130.

(4) (a) Frérot, E.; Bagnoud, A.; Vuilleumier, C. *Flavour Frag. J.* **2002**, *17*, 218−226. (b) Naf, F.; Velluz, A. *Flavour Fragr. J.* **1998**, *13*, 203−208.

(5) Mahmoud, S. S.; Croteau, R. B. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 14481−14486.

(6) Oishi, S.; Nelson, S. D. *J. Org. Chem.* **1992**, *57*, 2744−2747.

(7) *Herbal Medicine. Expanded Commission E Monographs*; American Botanical Council, 2000 (see: http://www.herbalgram.org/youngliving/HerbalMedicine/default.asp?m=65).

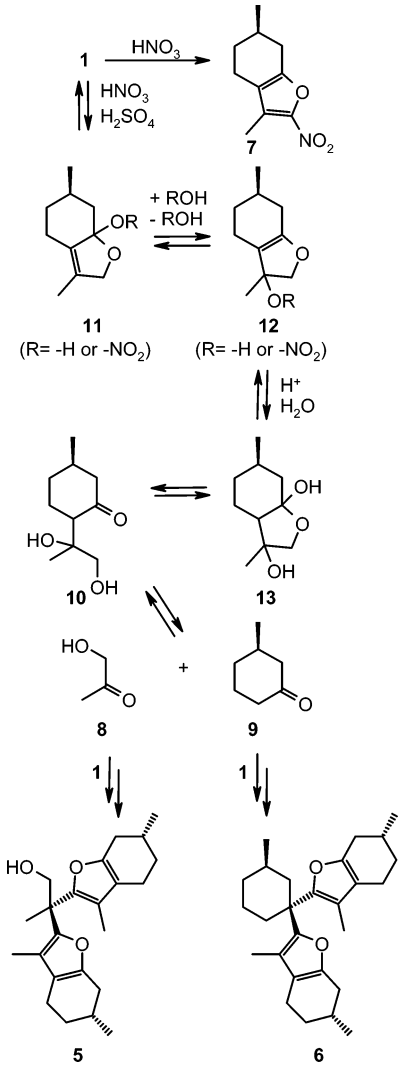
(8) d'Ischia, M.; Panzella, L.; Manini, P.; Napolitano, A. *Curr. Med. Chem.* **2006**, *13*, 3133−3144.

(9) (a) Ackman, R. G.; Brown, W. H.; Wright, G. F. *J. Org. Chem.* **1955**, *20*, 1147−1158. (b) Boyle, P. H.; Cocker, W.; McMurry, T. B. H.; Pratt, A. C. *J. Chem. Soc. C* **1967**, 1993−1998.

(10) Compound **6** obtained from *rac*-3-methylcyclohexanone is actually a mixture of diastereomers,[9b] due to the chirality of the two menthofuranyl moieties, but the NMR spectra of the compounds obtained from (*R*)-menthofuran and *rac*-3-methylcyclohexanone showed only minor differences in the splitting pattern of the ^{1}H NMR resonances, while their IR spectra were completely superimposable.

(11) The trapping reaction between **1** and carbonyl compounds is of general applicability and may lead to a variety of bisfuranyl adducts. For example, bisfuranyl adducts were easily obtained when **1** was treated with vanillin (54% yield), anisaldehyde (43%), and furfural (39%) in the presence of catalytic amounts of various acidic catalysts (H_2SO_4, *p*-toluenesulfonic acid, acidic Dowex resin). The reaction gives better yields with electron-rich carbonyl compounds, whereas no product was formed with benzaldehyde and aromatic aldehydes bearing electron-withdrawing groups (*o*- and *p*-nitrobenzaldehyde, *p*-chlorobenzaldehyde), suggesting that protonation of the aldehyde carbonyl group is the critical step. A more detailed account of this reaction is out of the scope of this paper and will be reported elsewhere.

SCHEME 1. Reactions of Menthofuran (1) with Nitric Acid: 5, 6, and 7 are Isolated Compounds and the Remainder are Postulated Intermediates



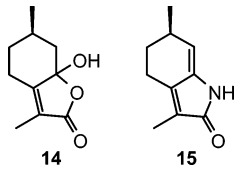
To provide evidence for a possible oxidative role for nitric acid, **1** was treated with a variety of oxidants, but formation of **5** and **6** could not be evidenced. Incidentally, during investigation of the reaction of **1** with different oxidizing systems, we noticed that, while transition-metal-based oxidants (PCC, PDC, tetrapropyl ammonium perruthenate (TPAP)) and oxone gave messy reaction mixtures, DDQ cleanly and reproducibly (ca. 40−45% yield) afforded the important fragrant monoterpenoid dehydromenthofurolactone (anhydro Woodward−Eastman lactone) **4**.[4] Surprisingly, this reaction has gone unreported in the abundant scientific and proprietary literature of **1** and is worth considering for further development on account of the relevance of **4** in perfumery and its metal-free conditions.[4] Lactone **4** is endowed with a pleasant and tenacious coumarinic smell and could also be obtained, albeit in lower yield (13%), by treatment of **1** with IBX (*o*-iodoxybenzoic acid).

Overall, available evidence indicates that nitric acid plays a specific role in the formation of **5** and **6**, which, however, does not involve the nitro derivative **7**, a compound stable under the reaction conditions. A tentative mechanism for the sulfuric acid catalyzed, nitric acid dependent formation of **5** and **6** is depicted in Scheme 1. According to this scheme, compounds **5** and **6** arise from the electrophilic trapping of the two carbonyl fragments, hydroxyacetone (**8**) and 3-methylcyclohexanone (**9**), by **1**. The observation that the 10 carbons of **1** are complementarily distributed between the alkylidene moieties of **5** and **6** suggests that the formation of **8** and **9** is mechanistically coupled.

The fragmentation step might be a relatively unsurprising acid-promoted retro-aldol cleavage of the β-hydroxycarbonyl derivative **10**, whose formation raises, however, interesting mechanistic issues. **10** might be formed from **1** by conjugated addition of nitric acid or water to the heterocyclic ring. Under these reaction conditions, α-protonation of the furan ring seemingly prevails over electrophilic addition of nitronium ion, generating a nitrate ester (or water addition product, **11**) that next affords, through a series of water (nitric acid) addition and eliminations steps (**12** and **13**), the seco-aldol **10**, eventually trapped as a bisfuranyl adduct by unprotonated starting material. With strong mineral acids (H_2SO_4, HCl, and $HClO_4$) or concentrated nitric acid, protonation of the furan moiety might be essentially quantitative, preventing nucleophilic trapping of the fragmentation products, a step that might well act as a steering sink for what is essentially a complex equilibrium between alternative reaction pathways. Conversely, with H_3PO_4, the conjugate addition product is apparently formed too slowly or, alternatively, reaction pathways different from the conversion to aldol **10** are preferentially activated, leading to a plethora of compounds that could not be characterized. This view is supported by the strong dependence of the reaction course from the concentration of HNO_3, with 40% (along with cat. H_2SO_4) being optimal for the formation of the bis-menthofuranylidene adducts.

The Reaction of 1 with Nitrous Acid. Exposure of **1** (5 mM in the organic phase) to $NaNO_2$ (3 mM) in a biphasic system consisting of 0.1 M phosphate buffer (pH 3.0)/CH_2Cl_2 4:1 v/v for 2.5 h resulted in the smooth conversion of the substrate to a complex mixture of products, three of which could be characterized. The least polar one was the Woodward−Eastman lactone **14**, while a nitrogen-containing more polar compound was identified as the lactam **15**, a new compound that we have named anhydro mentholactam. The structural assignment of **15** was backed up by MS (pseudomolecular ion peak at *m*/*z* 164 ($[M + H]^+$), corresponding to the molecular formula $C_{10}H_{13}NO$ (HRMS)) and NMR data (olefin proton resonances at δ 5.77 (H-7), and amide-like carbon resonance at δ 173.1 (C-2)).

The third compound displayed intense absorption maxima at



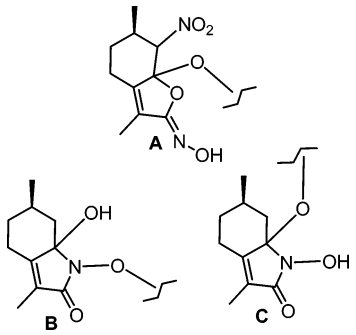
249 and 285 nm and a weak maximum at 364 nm, a pseudomolecular ion peak $[M + H]^+$ at *m*/*z* 422, and a molecular formula of $C_{20}H_{27}N_3O_7$ (HRMS), consistent with a menthofuran dimer bearing three nitrogen atoms.

The ^{1}H NMR spectrum exhibited two distinct sets of signals, corresponding to two substructures of the dimeric scaffold. One substructure showed a proton resonance at δ 5.08 (d, $J = 4.0$ Hz) cross-peak related (HSQC-DEPT spectrum) with a carbon resonance at δ 90.4. This proton resonance was coupled to a multiplet at δ 2.67, correlating in turn with a carbon signal at δ 33.1 and scalarly coupled to a methyl resonance at δ 1.08. Another diagnostic feature was the presence of two pairs of

diastereotopic methylene protons, one pair (δ 3.07 and 2.67) correlating with a carbon resonance at δ 22.2, and the other (δ 1.75 and 1.84) giving one-bond correlations with a carbon resonance at δ 27.5 and cross-peaks in the $^{1}H,^{13}C$ HMBC spectrum with four quaternary carbon resonances (δ 110.2, 127.3, 140.3, and 158.7).

The most prominent features of the second substructure were a deshielded methylene resonance at δ 45.0 in the ^{13}C NMR spectrum and a set of three quaternary carbon resonances at δ 173.0, 158.2, and δ 87.6, pointing to a substantial structural deviation from the menthofuran basic motif.

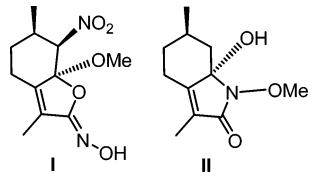
Since the proton and carbon NMR data could not provide conclusive insights into the nature of the nitrogen functionalities of the dimer, the reaction was carried out under identical conditions but using $Na^{15}NO_2$ as the nitrous acid source. The ESI+/MS spectrum of the dimer prepared in this way gave a pseudomolecular ion peak at *m*/*z* 425, consistent with the incorporation of three ^{15}N atoms. The $^{1}H,^{15}N$ HMBC spectrum revealed three nitrogen resonances at δ 195, 280, and 380. The upfield resonance, suggestive of an amide-type nitrogen, was assigned to the second structural unit based on the detection of a cross-peak with the allylic methyl of that unit. The other two nitrogen resonances were attributed to the first substructure on the basis of the following evidence: the signal at δ 380, typical of a nitro group, gave a cross-peak with the proton resonance at δ 5.08, whereas that at δ 280, compatible with an oxime-type functionality, correlated with the allylic CH_3 group of that moiety at δ 1.87. These spectroscopic data could be translated into a nitro-substituted 2-oximinofuran structure (**A**) for the first substructure and an O-substituted 1,7a-dihydroxy-2-pyrrolinone system for the second moiety, with both partial structures **B** and **C** being compatible with the NMR data.



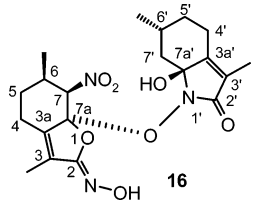
These substructures would exhibit different acidities since **B** is a hemi-aminal and **C** a hydroxamic acid and could be, in principle, distinguishable by methylation experiments with diazomethane. Thus, a compound made up of substructures **A** and **B** should give a monomethyl derivative, whereas a dimer built on **A** and **C** would instead afford a dimethyl derivative. LC-MS analysis indicated reaction product consistent with a monomethyl derivative, pointing to substructure **B** for the second moiety of the dimer.

To support this conclusion and select among the possible configurational options, a systematic computational effort aimed at simulating the NMR spectra for all possible model structures was carried out, using validated protocols based on DFT to calculate energies, geometries, and NMR chemical shifts.[12] Candidate structural models (listed in the Supporting Information) were geometry optimized at the DFT level, using the "hybrid" PBE0 functional,[13] which has been shown to provide quite satisfactory energies and geometries for a wide range of organic and biological systems,[14] as well as an accurate description of NMR parameters.[15] Solvent effects were considered in some test calculations using the polarizable continuum model (PCM, see Experimental Section) and were found to exert a marginal influence on computed carbon shifts, so that use of in vacuo calculations is justified.

The relatively large molecular size of the product and the number of diastereomers/conformers to be explored combine to make the quantum mechanical characterization computationally expensive. Therefore, a factorization of the problem was devised by analyzing the product into its two different moieties and using a methoxy group to mimic the inter-moiety link. For the **A** moiety, the configuration depicted in **I** corresponds to the best fulfillment of two criteria adopted to sort out the different structural possibilities, namely, the correlation coefficients between computed and experimental carbon shifts, and the maximum chemical shift deviation from a linear correlation (see Supporting Information). Moreover, the predicted value (55°) for the H6−C6−C7−H7 dihedral angle is compatible with the small scalar coupling (4.0 Hz) observed between H-6 and H-7. As far as the **B** moiety is concerned, a satisfactory agreement between experimental and theoretical NMR data was obtained with the O-substituted 1-hydroxy-2-pyrrolinone ring **II**.



The combination of the two moieties led to structure **16** for the dimeric compound. A full conformational exploration of **16** was then performed at the same PBE0/6-31+G(d,p) level. A linear correlation plot between computed and experimental carbon chemical shifts for the entire structure gave a correlation coefficient of 0.9996. Furthermore, the constitution and configuration of **16** were further validated by the detection of ROESY contacts between the H-7 methine (δ 5.08) and the H-7′ methylenes (δ 1.10 and 2.38), a finding computationally predicted for **16** but not for its 7a*R* diastereoisomer. A similar exploration was carried out for two other different diastereoisomers of **16**, and comparison with the available experimental information allowed us to dispel both alternatives (see Supporting Information).



NMR data assignments for **15** and **16** are reported in Table 1.

Interestingly, on exposure to aqueous NaOH, the chromophore of **16** underwent an irreversible bathochromic shift to 440 nm, suggesting a base-induced degradation, presumably

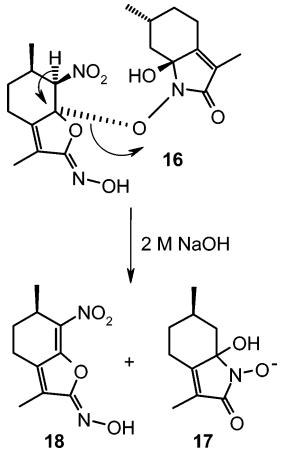
(12) (a) Barone, V.; Cimino, P.; Crescenzi, O.; Pavone, M. *THEOCHEM* **2007**, *811*, 323−335. (b) Benzi, C.; Crescenzi, O.; Pavone, M.; Barone, V. *Magn. Reson. Chem.* **2004**, *42*, S57−S67. (c) Barone, V.; Crescenzi, O.; Improta, R. *Quant. Struct.-Act. Relat.* **2002**, *21*, 105−118.

(13) Adamo, C.; Barone, V. *J. Chem. Phys.* **1999**, *110*, 6158−6170.

TABLE 1. NMR Spectral Data of 15 and 16 ($CDCl_3$)

	15			16			
	^{1}H (*J*, Hz)	^{13}C	^{15}N	^{1}H (*J*, Hz)	^{13}C	^{15}N	^{13}C, computed
1	–	–	126	–	–	–	
2	–	173.1	–	–	158.7	–	161.7
2-N	–	–	–	–		280	
3	–	136.6	–	–	127.3	–	132.1
3a	–	155.5	–	–	140.3	–	146.7
4	2.45 (m), 2.75 (m)	21.5	–	2.67 (d, 3.2), 3.07 (bs)	22.2	–	24.0
5	1.40 (m), 2.00 (m)	31.8	–	1.75 (m), 1.84 (m)	27.5	–	26.9
6	2.60 (m)	30.1	–	2.67 (m)	33.1	–	33.2
7	5.77 (d, 4.0)	115.8	–	5.08 (d, 4.0)	90.4		92.0
7-N	–	–	–	–	–	380	
7a	–	141.5	–	–	110.2	–	110.6
3-CH_3	1.87 (s)	8.1	-	1.87 (s)	8.5	–	7.5
6-CH_3	1.14 (d, 6.8)	21.4	-	1.08 (d, 6.8)	17.8	–	16.3
1′				–	–	195	
2′				–	173.0	–	175.3
3′				–	122.8	–	127.3
3a′				–	158.2	–	165.2
4′				2.37 (m), 2.57 (d, 3.2)	24.2	–	24.8
5′				0.97 (m), 1.97 (m)	36.2	–	37.2
6′				2.06 (m)	28.0	–	28.6
7′				1.10 (m), 2.38 (m)	45.0	–	45.1
7a′				–	87.6	–	87.1
3′-CH_3				1.74 (s)	7.9	–	7.3
6′-CH_3				0.98 (d, 6.8)	21.0	–	19.9

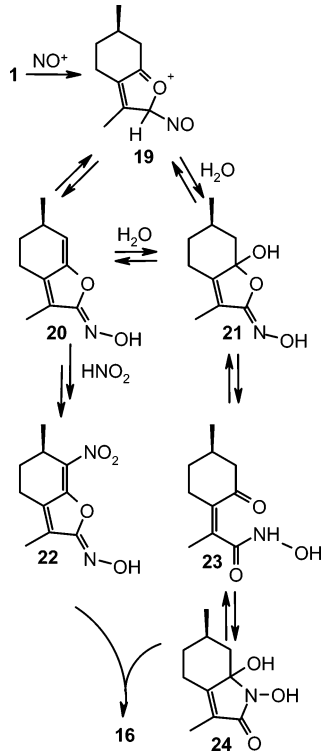
SCHEME 2. Mechanistic Rationalization for the Bathochromic Shift of the UV Spectrum of 16 in Alkaline Solution



expressed as a β-elimination reaction that generates, along with the hydroxamate **17**, the extensively conjugated nitro derivative **18** (Scheme 2). This view is consistent with the detection of two peaks with molecular weights corresponding to those of **17** and **18** in the LC-MS analysis of a UV bathochromically shifted alkaline solution of **16**.

A possible mechanism for the formation of **16** is outlined in Scheme 3. Attack of nitrosonium ion to the unsubstituted α-position of the furan ring could afford a σ intermediate (**19**) susceptible of pseudo-benzylic deprotonation or, alternatively, water trapping, affording eventually, after tautomerization of

SCHEME 3. Proposed Mechanism for the Formation of 16 by Reaction of 1 with Nitrous Acid



the nitroso group, the 2-oximinofuran derivatives **20** and **21**. The former can undergo further addition of nitrosonium ion to its enol moiety, generating, after nitroso-to-nitro oxidation and restoration of the double bond, the nitroolefin **22**. Conversely, the hemiketal **21** could generate an open ketohydroxamic acid (**23**), in equilibrium with its cyclic *N*-hydroxylactam tautomer (**24**). This might then add to the nitroolefin moiety of **22** in a Michael fashion, eventually affording **16**.

(14) (a) Benzi, C.; Improta, R.; Scalmani, G.; Barone, V. *J. Comput. Chem.* **2002**, *23*, 341−350. (b) Langella, E.; Rega, N.; Improta, R.; Crescenzi, O.; Barone, V. *J. Comput. Chem.* **2002**, *23*, 650−661. (c) Improta, R.; Mele, F.; Crescenzi, O.; Benzi, C.; Barone, V. *J. Am. Chem. Soc.* **2002**, *124*, 7857−7865.

(15) (a) Benzi, C.; Crescenzi, O.; Pavone, M.; Barone, V. *Magn. Reson. Chem.* **2004**, *42*, S57−S67. (b) Barone, V.; Crescenzi, O.; Improta, R. *Quant. Struct.-Act. Relat.* **2002**, *21*, 105−118.

This reaction sequence could also accommodate the formation of the lactone **14** from intermediate **23** since hydroxamic acids are hydrolyzed to carboxylic acids following exposure to nitrosating agents.[16] Lactam **15** might result from a more complex process involving dehydration of **24** and a deoxygenation step, possibly by redox exchange with some reaction intermediates, but this mechanism escaped elucidation.

Conclusions

We have reported the first comparative investigation of the reactions of **1**, an important, naturally occurring furan derivative found in various mint oils, with nitric acid and nitrous acid. In the presence of sulfuric acid, nitric acid induced mainly a fragmentation reaction of **1** into two carbonyl compounds eventually trapped by the unreacted starting material as bis-furanyl adducts. Considering the harsh reaction conditions and the notorious instability of **1** to acids, the yields of compounds **5** and **6** were relatively good and of potential preparative interest. Exposure of **1** to nitrous acid, on the other hand, led to a quite different pattern of products, including notably dimer **16**, featuring an unprecedented 2*H*-indol-2-one-1-oxyl-2*H*-benzo-[*b*]furan-2-one oxime structure with three different nitrogen functionalities. Structure **16** was elucidated by an integrated spectral and theoretical approach that highlights the powerful potential of ^{15}N NMR spectroscopy in combination with DFT methods for the elucidation of complex nitrogenous structures.

Although reports exist dealing with the nitration of furan derivatives,[17,18] the nitration and, especially, the nitrosation chemistry of 2,3,4-trisubstituted furans has remained virtually uncharted. The oxidative conversion of **1** to the important fragrant terpenoid dehydromenthofurolactone (anhydro Woodward−Eastman lactone) though rather low yielding is another interesting outcome of this study for its potential use as straightforward access route. A possible precedent for this chemistry may be found in previous work,[3] reporting the behavior of **1** in the presence of hepatic cytochromes P450 leading to mintlactones. The oxidizing activity of these cytochromes has been subsequently confirmed by other studies involving reaction with dimethyldioxirane.[6]

The results of this investigation may have also some implication in the fields of biological and medicinal chemistry. Interestingly, 3-methylcyclohexanone (**9**), a key intermediate in the reaction of **1** with nitric acid, has also been reported as a metabolite of **1**,[19] suggesting that even reaction pathways observed under nonphysiological conditions (nitric acid in the presence of sulfuric acid) might have biological relevance. Nitrosating species are involved in many endogenous physiological and pathological processes[8] so that some of the compounds isolated in this reaction may be real metabolites of **1** in living systems under different conditions. Since polysubstituted furans occur in many popular medicinal, dietary, and aromatic plants, a systematic investigation of the behavior of these naturally occurring furans with nitrating and nitrosating agents seems worth pursuing to complement the information available from metabolic studies.

Experimental Section

Reaction of 1 with HNO_3/cat. H_2SO_4. Isolation of 2,2-Bis-[(*R*)-3,6-dimethyl-4,5,6,7-tetrahydrobenzofuran-2-yl]propan-1-ol (5), (6*R*,6′*R*)-2,2′-[(*R*)-3-Methylcyclohexane-1,1-diyl]bis-3,6-dimethyl-4,5,6,6-tetrahydrobenzofuran (6), and (*R*)-3,6-Dimethyl-2-nitro-4,5,6,7-tetrahydrobenzofuran (7). To a cooled (5 °C) solution of **1** (485 mg, 3.22 mmol) in CH_2Cl_2 (2 mL) were added 40% HNO_3 (≤0.1% nitrogen oxides content, 1 mL) and H_2SO_4 (2 drops), resulting in the instantaneous development of a purple color. After 2 h, the reaction was quenched by the addition of sat. $NaHCO_3$ (15 mL) and extracted with petroleum ether. After washing with brine and evaporation, the crystalline residue was purified by gravity column chromatography on silica gel (petroleum ether/ethyl acetate 9:1 as the eluant) to afford crude **5** and **6** as brownish powders. Recrystallization from petroleum ether afforded as colorless material **5** (108 mg, 28% yield, >98% purity) and **6** (167 mg, 39% yield, >98% purity). In other experiments, the reaction of **1** was run as above but using 20% HNO_3. Purification of the reaction mixture by gravity column chromatography (petroleum ether/ethyl acetate 95:5 as the eluant) afforded **14** (100 mg, 18% yield, >95% purity) along with **5** (22 mg, 5% yield) and **6** (32 mg, 7% yield).

5: White powder (hexane), mp 98 °C (hexane); $[\alpha]^{25}_D$ +62 (*c* 0.90, $CHCl_3$); IR (KBr) (ν_{max}, cm^{-1}) 3400, 1770, 1714, 1681, 1650, 1574, 1455, 1378, 1291, 1223, 1032; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (6′-CH_3, d, J = 6.4 Hz), 1.37 (H-4b′, m), 1.58 and 1.60 (3′-CH_3, s), 1.68 (H-3, s), 1.84 (H-4a′, m), 1.91 (H-6′, m), 2.17 (H-7b′, m), 2.30 (H-5a,b′, m), 2.65 (H-7a′, dd, J = 15.9, 5.5 Hz), 3.94 (H-1, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.11 and 8.15 (2 × 3′-CH_3), 20.1 (CH_2, C-4′), 21.57 (CH_3, C-3), 21.60 (6′-CH_3), 29.8 (CH, C-6′), 31.4 (CH_2, C-5′), 31.4 (CH_2, C-7′), 44.3 (C, C-2), 69.2 (CH_2, C-1), 115.29 and 115.35 (C, 2 × C-3′), 118.7 (C, C-3a′), 147.6 (C, C-7a′), 148.8 (C, C-2′); HR ESI+/MS *m*/*z* 379.2220 ([M + Na]$^+$), calcd for $C_{23}H_{32}NaO_3$ *m*/*z* 379.2249.

6:[9b] Colorless needles, mp 135 °C (lit. 130 °C[9b]); IR (KBr) (ν_{max}, cm^{-1}) 1670, 1454, 1376, 1223, 1111, 868 (lit. 1640[9b]); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (d, J = 6.5 Hz, 3H), 0.95 (m, 1H), 1.05 and 1.08 (d, J = 6.5 Hz, 2 × 3H), 1.34 (s, 3H), 1.38−1.42 (m, 2H), 1.50−1.65 (m, 6H), 1.84 (s, 3H), 1.70−1.95 (m, 4H), 2.05−2.18 (m, 2H), 2.20−2.35 (m, 4H), 2.48 (m, 2H), 2.66 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.2 (CH_3), 9.1 (CH_3), 20.2 (CH_2), 20.3 (CH_2), 21.6 (CH_3), 21.8 (CH_3), 22.8 (CH), 23.1 (CH_2), 28.8 (CH_3), 29.8 (2 × CH), 31.5 (4 × CH_2), 34.3 (CH_2), 34.8 (CH_2), 43.0 (CH_2), 43.8 (C), 112.6 (C), 115.0 (C), 118.6 (C), 120.0 (C), 146.7 (C), 146.9 (C), 149.0 (C), 152.9 (C); HR ESI+/MS *m*/*z* 417.2791 ([M + Na]$^+$), calcd for $C_{27}H_{38}NaO_2$ *m*/*z* 417.2770.

7: Foam, $[\alpha]^{25}_D$ +11 (*c* 0.90, MeOH); IR (KBr) (ν_{max}, cm^{-1}) 1616, 1551, 1484, 1374, 1293, 1233, 1118; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (6-CH_3, d, J = 6.4 Hz), 1.40 (H-4b, m), 1.84 (H-4a, m), 2.00 (H-6, m), 2.23 (H-7b, dd, J = 17.8, 9.8 Hz), 2.34 (3-CH_3, br s), 2.40 (H-5a,b, m), 2.75 (H-7a, dd, J = 17.8, 5.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.5 (3-CH_3), 19.6 (CH_2, C-4), 21.2 (6-CH_3), 29.1 (CH, C-6), 30.3 and 31.2 (CH_2, C-5 and C-7), 122.5 (C, C-3a), 126.4 (C, C-3), 145.0 (C, C-2), 154.5 (C, C-7a, C); HR ESI+/MS *m*/*z* 196.0985 ([M + H]$^+$), calcd for $C_{10}H_{14}NO_3$ *m*/*z* 196. 0974.

Preparation of Bismenthofuranylidene Adducts 5 and 6. To a solution of **1** in toluene (2.5 mL/mmol) were added the carbonyl compound, hydroxyacetone for **5** and *rac*-3-methylcyclohexanone for **6** (0.5 equiv), and one drop of concd H_2SO_4 (or 10 mg/mmol acidic Dowex resin). After stirring at rt for 12−48 h, the reaction was worked up by washing with sat. $NaHCO_3$ (or filtration for Dowex removal), and the filtrate was concentrated. The adduct was purified by crystallization from hexane or, alternatively, by gravity column chromatography. The yields were 45% for **5** and 52% for **6**.

Oxidation of 1 with DDQ. Isolation of (*R*)-3,6-Dimethyl-5,6-dihydrobenzofuran-2(4*H*)-one (Dehydromenthofurolactone, an-

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hydro Woodward−Eastman Lactone, 4). To a solution of **1** (200 mg, 1.33 mmol) in acetonitrile (6 mL) was added DDQ (605 mg, 2.66 mmol, 2 molar equiv). After stirring at rt for 1 h, the reaction was worked up by filtration over Celite. The filtration cake was washed with acetonitrile, and the pooled filtrates were evaporated. The residue was purified by gravity column chromatography on silica gel (hexane/ethyl acetate 8:2 as the eluant) to afford **4** (97 mg, 44% yield) as a colorless oil.

4: Oil, IR (liquid film) (ν_{max}, cm^{-1}) 1735, 1661, 1445, 1327, 1259, 1212, 1113; ^1H NMR (400 MHz, $CDCl_3$) δ 1.14 (d, $J = 6.4$ Hz, 3H), 1.48 (m, 1H), 1.87 (br s, 3H), 1.95 (m, 1H), 2.49 (m, 1H), 2.59 (m, 1H), 2.71 (dt, $J = 16.5$, 5.0 Hz, 1H), 5.60 (d, $J = 4.1$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.4 (CH_3), 21.2 (CH_3), 21.9 (CH_2), 29.8 (CH), 31.0 (CH_2), 114.1 (CH), 119.8 (C), 148.2 (C), 149.2 (C), 171.6 (C); HR ESI+/MS *m*/*z* 165.0908 ($[M + H]^+$), calcd for $C_{10}H_{13}O_2$ *m*/*z* 165.0916.

Reaction of 1 with Nitrite. To a solution of **1** (10 mg, 67 μmol) in dichloromethane (14 mL) was added 0.1 M phosphate buffer (pH 3.0, 56 mL) (1:4 v/v, with respect to the organic layer), followed by sodium nitrite (14 mg, 203 μmol), and the biphasic system was taken under vigorous stirring at rt. After 2 h and 30 min, the organic layer was separated, the aqueous phase was washed with dichloromethane (3 × 15 mL), and the combined organic layers were dried over sodium sulfate and taken to dryness. The residue was analyzed by TLC (eluant cyclohexane/ethyl acetate 1:1) and LC-MS. When required, $Na^{15}NO_2$ was used in the reaction of **1** with nitrite, and the mixture was worked up and analyzed as above. In other experiments, the reaction of **1** was run as above but with purging of the biphasic system with argon for at least 30 min prior to the addition of sodium nitrite. In control experiments, the reaction was carried out under the conditions of the general procedure without added nitrite.

Isolation of 5,6,7,7a-Tetrahydro-7a-hydroxy-3,6-dimethyl-4*H*-benzofuran-2-one (14), 1,4,5,6-Tetrahydro-3,6-dimethyl-2*H*-indol-2-one (15), and (*Z*)-(6*R*,7*R*,7a*S*)-4,5,6,7-Tetrahydro-7a-[(6*R*,7a*S*)-4′,5′,6′,7′-tetrahydro-7a′-hydroxy-3′,6′-dimethyl-2*H*-indol-2-one-1-oxyl)]-3,6-dimethyl-7-nitro-2*H*-benzo[*b*]furan-2-one oxime (16). For preparative purposes, the reaction of **1** with $NaNO_2$ or $Na^{15}NO_2$ was carried out as described in the general procedure using 1 g of the starting material. After work up of the reaction mixture, the residue (1 g) was fractionated by silica gel column chromatography (3 cm × 85 cm) using petroleum ether/ethyl acetate (40:60) with 0.5% acetic acid as the eluant (8:2 to 4:6 gradient mixtures) to give nine fractions. Fractions V, VI, and VII were purified on preparative TLC using chloroform/ethyl acetate 1:1 as eluant to give **14**[4a] (R_f 0.67, 12 mg, 1% yield, >95% purity), **15** (R_f 0.44, 11 mg, 1% yield, >95% purity), and **16** (R_f 0.55, 28 mg, 1% yield, >95% purity).

15: $[\alpha]^{25}_D$ +21.5 (*c* 0.79, $CHCl_3$); UV λ_{max} (CH_3OH) 277 nm; IR ($CHCl_3$) (ν_{max}, cm^{-1}) 2926, 2869, 1775, 1703, 1558, 1458, 1377, 1346, 1309, 1140; HR ESI+/MS *m*/*z* 164.1066 ($[M + H]^+$), calcd for $C_{10}H_{14}NO$ *m*/*z* 164.1075; ^1H, ^{13}C NMR, and ^{15}N data, see Table 1.

16: $[\alpha]^{25}_D$ −12.0 (*c* 0.59, $CHCl_3$); UV λ_{max} (CH_3OH) 249, 285, 364 nm; IR ($CHCl_3$) (ν_{max}, cm^{-1}) 2928, 2853, 1726, 1678, 1558, 1461, 1383, 1156; HR ESI+/MS *m*/*z* 422.1921 ($[M + H]^+$), calcd for $C_{20}H_{28}N_3O_7$ *m*/*z* 422.1927; *m*/*z* 444.1736 ($[M + Na]^+$), calcd for $C_{20}H_{27}N_3O_7Na$ *m*/*z* 444.1747; ^1H, ^{13}C NMR, and ^{15}N data, see Table 1.

Compound **16** was treated with diazomethane and analyzed by TLC and LC-MS. In other experiments, **16** was treated with 2 M NaOH and the reaction mixture analyzed by LC-MS.

Quantum Mechanical Computations. All calculations were performed with the Gaussian 03 suite.[20] The 6-31+G(d,p) basis set[21] was adopted for geometry optimization, while NMR shielding tensors were computed within the gauge-including atomic orbitals (GIAO) ansatz[22] at the PBE0/6-311+G(d,p) level. Computed isotropic shieldings were converted into chemical shifts using as reference the values obtained at the same level for cyclohexane ($\delta_C = 27.10$, $\delta_H = 1.429$, in $CDCl_3$).[23]

Although large solvent effects on solute geometries and spectroscopic parameters are not expected in the relatively apolar $CDCl_3$ solutions, some test calculations were carried out using the polarizable continuum model (PCM)[24] to simulate the influence of the solvent. In the PCM approach, the solvent is represented by an infinite dielectric medium characterized by the relative dielectric constant of the bulk, and a set of optimized radii (in the present instance, the UAHF radii)[25] are used to build an effective cavity occupied by the solute within the solvent. In particular, geometry optimization and computation of NMR parameters were repeated in the presence of the PCM for the three most stable conformers of **16**, and the resulting averaged chemical shifts were compared with those obtained in vacuo. However, changes in computed carbon shifts are smaller than 1.4 ppm, and the correlation coefficient between experimental and computed carbon shifts is 0.99962 (versus 0.99965 in vacuo).

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Supporting Information Available: General experimental methods; ^1H NMR spectra of compounds **5**−**7** and **14**−**16**; ^{13}C NMR, ^1H, ^1H COSY, ^1H, ^{13}C HSQC-DEPT, ^1H, ^{13}C HMBC, ^1H, ^{15}N HMBC spectra of compounds **15** and **16**; ROESY and DQF-COSY spectra of compound **16**; computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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