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ISOLATION AND IDENTIFICATION OF 2,3-DIMETHYL-6-(4,8,12-TRIMETHYLTRIDECYL)-1,4-NAPHTHOQUINONE FROM TOBACCO AND SMOKE

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A previously undescribed quinone has been isolated from low alkaloid bright tobacco filler as a result of our continuing effort to identify new components from tobacco and smoke. This compound, 2,3-dimethyl-6-(4,8,12-trimethyltridecyl)-1,4-naphthoquinone (solanoquinone[†], **4**) appears to be the first example of a naturally occurring quinone with a saturated polyisoprenoid side chain.

The isolation procedure involved an initial hexane extraction of 970 g of low alkaloid bright strip. The extract residue was partitioned between cyclohexane and methanol/water (9:1, v:v), followed by repartitioning of the cyclohexane residue with cyclohexane and nitromethane. Silica gel column chromatography of the nitromethane residue with benzene/cyclohexane (3:2, v:v) as solvent gave a fraction (3.5 mg) from which 120 μg of **4** was isolated. Although more of **4** partitions into the cyclohexane layer rather than into the nitromethane layer, the cyclohexane layer contains a number of lipids with gc retention times similar to **4**. As a consequence, no further work was done with the cyclohexane layer with regard to gas chromatography. An alternative procedure useful for isolating microgram amounts of **4** is achieved by subjecting the residue from the hexane extraction of filler to preparative tlc using silica gel plates with a fluorescing indicator and developing with benzene/cyclohexane (3:2, v:v). Visualization with short wavelength uv produces a quenching zone (R_f = 0.5).

Analysis of the mass spectrum of **4** shows the parent ion as the base peak, a feature common to phylloquinone[1] (present in the same fraction as **4**). Precise mass measurements gave a molecular formula of $C_{28}H_{42}O_2$ (calculated: 410.3184; found: 410.3188, 100%, base peak). Ions corresponding to loss of alkyl radicals from the side chain with charge retention by the aromatic ring moiety are evidence for the saturated side chain. These ions occur at m/e 395 ($C_{27}H_{39}O_2$, 0.4%), m/e 325 ($C_{22}H_{29}O_2$, 0.7%), m/e 283 ($C_{19}H_{23}O_2$, 0.4%), m/e 269 ($C_{18}H_{21}O_2$, 0.7%), m/e 255 ($C_{17}H_{19}O_2$, 2.5%), m/e 227 ($C_{15}H_{15}O_2$, 1.7%), m/e 213 ($C_{14}H_{13}O_2$, 2.6%), and m/e 199 ($C_{13}H_{11}O_2$, 8.2%). Also present is a rearrangement ion at m/e 200 ($C_{13}H_{12}O_2$, 10.6%), probably resulting from hydrogen transfer from the side chain to a quinone oxygen. Ions characteristic of quinones[2] are present,

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[†] The compound was named on the basis of its occurrence in *Nicotiana tabacum* (a member of the *solanaceae* family).

probably originating from the ion at m/e 199. These ions correspond to loss of one and two molecules of CO to give m/e 171 ($C_{12}H_{11}O$, 2.8%) and m/e 143 ($C_{11}H_{11}$, 0.3%), respectively.

Other spectral data support the structure assignment. The uv maxima (in hexane) occur at 248, 255, 262, 272, and 330 nm with log ε values of 4.51, 4.54, 4.43, 4.44, and 3.60, respectively. The large extinction coefficients are characteristic of substituted naphthoquinones such as the K vitamins.[3] Assignments in the ir include (in cm^{-1}) 2960, 2924, 2860 (aliphatic C-H), 1664 (quinone$>$C = O), 1625, 1605 (aromatic$>$C = C$<$), 1462 ($-CH_2-$), 1378 ($-CH_3$), 1305 (aromatic ketone), and 720,695 (substituted aromatic ring).

The ^1H-NMR data are shown in Table 1. The coupling constants for the aromatic proton resonances at 7.51, 7.91, and 8.00 ppm suggested a 1,3,4-trisubstituted aromatic ring, since ortho and meta coupling constants are about 8 Hz and 2 Hz, respectively. The triplet at 2.72 ppm (J = 8 Hz) was consistent with methylene protons of a hydrocarbon attached to an aromatic ring. The sharp singlet at 2.18 ppm was consistent with two methyl groups attached to a carbon-carbon double bond with no α or β protons. The broad multiplet (1.0-1.86 ppm) with 19 protons was consistent with a long chain hydrocarbon. The doublet at 0.86 ppm (12 protons) was consistent with four methyl groups attached to methine carbons contained in an aliphatic side chain. Since spectral evidence indicated that quinone carbonyls were present in the molecule, the fragments were assembled to give the aliphatic substituent at the 6 position on the ring.*

Table 1: Proton NMR data for solanoquinone

position (ppm)	coupling constant (Hz)	multiplicity	integral	assignment
0.86	6	doublet	12 H	4 methyl groups of side chain
1.0-1.86	-	multiplet	19 H	$-CH_2-$ and tertiary -CH of side chain
2.18	-	singlet	6 H	2 quinone methyl groups
2.72	8	triplet	2 H	$-CH_2-$ at C-6 of naphthoquinone
7.51	8, 2	doublet of doublet	3 H	low field aromatic protons
7.91	2	doublet		
8.00	8	doublet		

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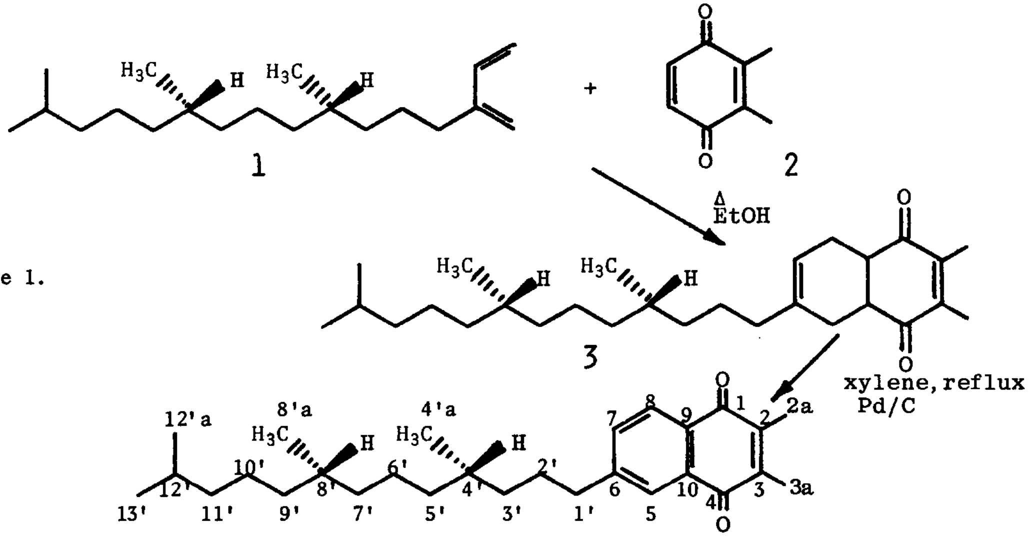
*The same substitution pattern is seen in 2,3,6-trimethyl-1,4-naphthoquinone which has been reported to be present in tobacco[4] and smoke.[5]

Final confirmation of the proposed structure of 4 was accomplished by its synthesis (Scheme 1). The 2,3-dimethylbenzoquinone (2) was prepared from 2,3-dimethylphenol.[6] Neophytadiene (1) was prepared by base catalyzed dehydration of natural phytol.[7] The synthesis and stereochemistry of phytol was reported by Weedon *et al.*,[8] so this provides a total synthesis of 4. The Diels-Alder reaction of 1 and 2 (ratio 1 to 1.1) was carried out in refluxing ethanol. The presumed tetrahydronaphthoquinone (3) was not isolated, but was dehydrogenated directly by refluxing it in xylene over palladium on carbon. The dehydrogenated Diels-Alder adduct was isolated in 35% yield *via* preparative tlc. The spectral data from the final product (4) were identical in all respects to the material isolated from tobacco.*

Scheme 1.



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The synthetic solanoquinone was used to assign chemical shift values for carbon-13 NMR, since we have not been able to isolate the compound from tobacco in sufficient quantity for this analysis. These assignments are given in Table 2. The numbering system used for the aliphatic side chain is the same as that used by Matsuo and Urano[9] in a ^{13}C-NMR analysis of tocopherols. Since the aliphatic side chain in the tocopherols is identical to that in the solanoquinone, we were able to make the assignments shown. The values in brackets are Matsuo and Urano's values for these carbons. Except for the 1' and 2' positions, which involve different chemical environments than the tocopherols, the agreement is excellent. The naphthoquinone assignments were made by comparison with model compounds.[10]

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*Two side products were identified: 2,3-dimethyl-1, 4-hydroquinone (5) 20%, and 2,3,7,8-tetramethyl-5-(2,6,10-trimethylundecyl)-1,4-naphthoquinone (6) 12%.

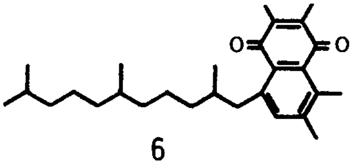

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Table 2. Carbon 13-NMR data for synthetic solanoquinone (4)

Carbon No.	^{13}C chemical^a shift (ppm)	
1,4	184.99 184.56	
6	149.10	
2, 3	143.18 143.02	
7	133.28	
9,10	131.99 130.00	
5,8	126.34 125.86	
11'	39.39	[39.4]
1', 3', 5', 7', 9'	37.45 37.34 (2) 36.59 36.49	[37.5]
4', 8'	32.82 32.72	[32.7]
2'	28.57	[21.0]
12'	28.04	[28.0]
10'	24.86	[24.8]
6'	24.48	[24.5]
12'a, 13'	22.76 22.71	[22.6]
8'a, 4'a	19.80 19.75	[19.7]
2a, 3a	12.92 (2)	

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[a] values in brackets [] from reference 9

Quantitation of 4 from bright tobacco shows an increase of the compound with flue-curing. The level of 4 in a sample of freeze-dried green lamina was found to be 40 x 10^{-3} µg/g. Flue-curing of the sample increased the level to 90 µg/g, indicating that reactions are occurring in the leaf curing to produce 4. The structural relationship between the side chain of 4 and neophytadiene is probably more than coincidental since neophytadiene is known to be a major constituent of cured leaf;[11] consequently, we have assumed that the absolute configuration of the side chain in solanoquinone is identical to that of neophytadiene. This point will be pursued.

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