with **3b** as starting material. The product (thick oil) isolated after flash chromatography was crystallized from Et_2O to give **5b**: mp 109–110 °C; 20% yield; ^1H NMR ($CDCl_3$) δ 7.50 (A_2B_2, q, 4 H, J = 8 Hz, $\Delta\nu_{AB}$ = 25 Hz, Ar H), 6.75 (br s, NH), 4.90 (m, 2 H, CH_2CHCH_3), 3.36 (m, 2 H, $NHCH_2CH$), 2.4 (s, 3 H, $CH_3C_6H_4$), 2.0 (s, 2 H, $CH_3C{=}O$), 1.15 (d, 3 H, J = 6 Hz, $CHCH_3$). Anal. Calcd for $C_{13}H_{18}N_2O_5S$: C, 49.67; H, 5.77; N, 8.91. Found: C, 49.90; H, 5.81; N, 8.86. The early chromatographic fractions contained **7b** as determined by TLC [silica gel, EtOAc/hexane-/AcOH (100:100:1)].

Reaction of 1a with Trifluoroacetic Anhydride. In a NMR Tube. **1a** (46.4 mg, 0.214 mmol) was dissolved in 0.5 mL of $CDCl_3$, and the ^1H NMR spectrum was determined. After addition of trifluoroacetic anhydride (62.5 mg, 0.297 mmol), the spectra were recorded at 5 min and periodically thereafter over 18.5 h. The triplet due to the NH proton gradually disappeared over several hours, and the aromatic protons shifted away from Me_4Si. Some solids had precipitated after 18.5 h and were redissolved by gentle warming on the steam bath: ^1H NMR (18.5 h) δ 7.72 (A_2B_2, q, J = 8 Hz, $\Delta\nu_{AB}$ = 29 Hz), 3.30 (m), 1.62 (m), 0.93 (t, J = 6 Hz).

Preparative Scale. **1a** (1.39 g, 5.02 mmol) was dissolved in 10 mL of chloroform, and, with stirring, trifluoroacetic anhydride (2.0 mL, 3.0 g, 14 mmol) was added all at once. After 1.5 h, the precipitated solids were collected to give 1.36 g (94% yield) of **8a**, mp 157–159 °C with sublimination earlier. Recrystallization from chloroform gave a product with mp 158–159 °C (colorless needles): ^1H NMR ($CDCl_3$) δ 7.77 (A_2B_2, q, 4 H, J = 8 Hz, $\Delta\nu_{AB}$ = 31 Hz, Ar H); IR (KBr) 3230 (NH), 1785 (C=O), 1590 (Ar C=C), 1470, 1360, 1300, 1220–1080 (six bands), 1020, 890, 830, 820, 810, 760, 620 cm^{-1}. Anal. Calcd for $C_8H_5ClF_3NO_3S$: C, 33.41; H, 1.75; N, 4.87. Found: C, 33.34; H, 1.80; N, 4.84. The mp and NMR and IR spectra of **8a** prepared by trifluoroacetylation of **6a** were identical with those of the above product.

With tolbutamide, **8b** was isolated in 62% yield: mp 151–152 °C; ^1H NMR ($CDCl_3$) δ 7.75 (A_2B_2, q, 4 H, J = 8 Hz, $\Delta\nu_{AB}$ = 38 Hz, Ar H), 2.48 (s, 3 H, $CH_3C_6H_4$); IR (KBr) 3220 (br, NH), 1770 (C=O), 1595 (Ar C=C), 1455, 1360, 1290, 1220–1080 (six bands), 880, 820, 790, 650 cm^{-1}. This product was identical with **8b** prepared by trifluoroacetylation of **6b**, mp 152–153 °C. Anal. Calcd for $C_9H_8F_3NO_3S$: C, 40.45; H, 3.02; N, 5.42. Found: C, 40.74; H, 3.03; N, 5.26.

1-[(4-Chlorophenyl)sulfonyl]-3-cyclohexylurea (9). Prepared from 4-chlorobenzenesulfonamide and cyclohexyl isocyanate by using the procedure for **1b** above: mp 159–161 °C [lit.[14] mp 158–159 °C); ^1H NMR ($CDCl_3$) δ 7.62 (A_2B_2, q, J = 4 Hz, $\Delta\nu_{AB}$ = 25 Hz, Ar H), 3.58 (m, 1 H, NHCH), 1.50 (m, 10 H, c-C_6H_{11}).

Acetylative Cleavage of 9. To the sodium salt of compound **9** prepared from **9** (3.20 g, 10.0 mol) and 0.67 g of NaH (50% suspension, 0.014 mol) in 300 mL of sodium-dried benzene was added at room temperature 1.0 mL (0.014 mol) of acetyl chloride in 20 mL of dry benzene. After the mixture was heated under reflux for 3 h cyclohexylamine (2.2 mL, 0.20 mol) was added, and the solvent was evaporated in vacuo. The residual semisolids were slurried in 150 mL of H_2O, and the mixture was extracted with 4 × 300 mL of EtOAc. The combined EtOAc extract was warmed and dried quickly over anhydrous Na_2SO_4, and the solvent was evaporated to approximately 20% of the original volume. The solids that had precipitated were recrystallized by addition of methanol and heating to give 1.34 g (60% yield) of dicyclohexylurea, mp 232–234 °C, identical with an authentic sample with respect to IR and NMR spectra and TLC mobility. Workup of the mother liquor afforded 1.34 g (57% yield) of **7a**, mp 195–197 °C, whose NMR spectrum and TLC mobility were identical with those of an authentic **7a**. In a separate run, a 5-mL aliquot of the heated reaction mixture was evaporated to incipient dryness, and the residue was taken up in 10 mL of CH_2Cl_2. Addition of 15 mL of hexane precipitated some solids, which were removed by filtration. The IR spectrum of the filtrate showed a characteristic isocyanate band at 2230 cm^{-1}.

1-[(4-Chlorophenyl)sulfonyl]-3-methyl-3-(*n*-propyl)urea (10). Prepared by reaction of 4-chlorobenzenesulfonyl isocyanate (8.5 mL, 60 mmol) and *N*-methyl-*n*-propylamine (4.0 g, 54 mmol) in 30 mL of benzene at room temperature overnight. The reaction mixture was extracted with 100 mL of 0.2 N HCl, and the separated benzene layer was dried (Na_2SO_4) and evaporated to incipient dryness. Recrystallization of the solid residue from EtOAc/hexane gave 10.4 g (66% yield) of crystalline **10**: mp 131–133 °C; ^1H NMR ($CDCl_3$) δ 7.66 (A_2B_2, q, 4 H, J = 8 Hz, $\Delta\nu_{AB}$ = 31 Hz, Ar H), 3.10 (t, 2 H, J = 7 Hz, NCH_2CH_2), 2.90 (s, 3 H, NCH_3), 1.50 (m, 2 H, $CH_2CH_2CH_3$), 0.80 (t, 3 H, J = 8 Hz, CH_2CH_3). Anal. Calcd for $C_{11}H_{15}N_2ClO_3S$: C, 45.44; H, 5.20; N, 9.63. Found: C, 45.07; H, 5.28; N, 9.50.

1-Acetyl-1-[(4-chlorophenyl)sulfonyl]-3-methyl-3-(*n*-propyl)urea (11). Compound **10** (2.90 g, 10.0 mmol) in a mixture of 100 mL of anhydrous Et_2O, 25 mL of dry THF, and triethylamine (1.67 mL, 12.0 mmol) was acetylated with acetyl chloride (0.86 mL, 12 mmol) at ice bath temperature. After a standard workup procedure, the crude product, a thick liquid, was crystallized from Et_2O/hexane to give 2.00 g (61.0% yield) of colorless powder: mp 92 - 94 °C; ^1H NMR ($CDCl_3$) δ 7.78 (A_2B_2, q, 4 H, J = 8 Hz, $\Delta\nu_{AB}$ = 35 Hz, Ar H), 3.48 (t, 2 H, J = 8 Hz, NCH_2CH_2), 3.11, 3.23 (2 s, 3 H, NCH_3), 2.12 (s, 3 H, $CH_3C{=}O$), 1.72 (m, 2 H, $CH_2CH_2CH_3$), 1.00 (t, 3 H, J = 7 Hz, CH_2CH_3). Anal. Calcd for $C_{13}H_{17}N_2ClO_4S$: C, 46.92; H, 5.15; N, 8.42. Found: C 46,73; H, 4.97; N, 8.24.

1-Methyl-1-[(4-chlorophenyl)sulfonyl]-3-(*n*-propyl)urea (12). Prepared by reaction of *N*-methyl-4-chlorobenzenesulfonamide (6.17 g, 30.0 mmol) and *n*-propyl isocyanate (3.70 mL, 40.0 mmol) in the presence of triethylamine (4.90 mL, 35.0 mmol) (overnight at room temperature) to give crude **13** as a yellow oil. Purification by chromatography on a silica gel column using EtOAc as eluent gave 7.2 g (83% yield) of pale yellow liquid (lit.[6b] oil, by methylation of **1a**): ^1H NMR ($CDCl_3$) δ 7.59 (A_2B_2, q, 4 H, J = 8 Hz, $\Delta\nu_{AB}$ = 15 Hz, Ar H), 7.22 (br m, 1 H, NH), 3.20 (*q*, 2 H, J = 7 Hz, $NHCH_2CH_2$), 3.12 (s, 3 H, NCH_3), 1.55 (m, 2 H, $CH_2CH_2CH_3$), 0.92 (t, 3 H, J = 8 Hz, CH_2CH_3). Anal. Calcd for $C_{11}H_{15}N_2ClO_3s$: C, 45.44; H, 5.20; N, 9.63. Found: C, 45.79; H, 5.39; N, 9.52.

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Registry No. **1a**, 94-20-2; **1b**, 24570-88-5; **2a**, 36892-35-0; **2b**, 98922-54-4; **3a**, 36892-36-1; **3b**, 75483-15-7; **4a**, 98043-39-1; **4b**, 98043-41-5; **5a**, 98922-55-5; **5b**, 98922-56-6; **6a**, 98-64-6; **6b**, 70-55-3; **7a**, 55379-05-0; **7b**, 1888-33-1; **8a**, 98922-57-7; **8b**, 81005-28-9; **9**, 963-03-1; **10**, 98922-58-8; **11**, 98922-59-9; **12**, 60153-02-8; *p*-toluenesulfonamide, 70-55-3; *n*-propyl isocyanate, 110-78-1; 4-chlorobenzenesulfonyl isocyanate, 5769-15-3; 3-aminopropan-1-ol, 156-87-6; *p*-toluenesulfonyl isocyanate, 4083-64-1; 1-aminopropan-2-ol, 78-96-6; tolbutamide, 64-77-7; cyclohexyl isocyanate, 3173-53-3; cyclohexylamine, 108-91-8; dicyclohexylurea, 2387-23-7; *N*-methyl-*n*-propylamine, 627-35-0; *N*-methyl-4-chlorobenzenesulfonamide, 6333-79-5.

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Synthesis of the Naturally Occurring Antioxidant Rosmariquinone

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Recently Houlihan, Ho, and Chang reported the isolation from rosemary leaves of a norditerpene, rosmariquinone, which showed antioxidant behavior comparable to that of the commonly used phenolics BHT and BHA.[1] Based on IR, NMR, and mass spectra they proposed the orthonaphthoquinone structure **1**, which is unique among naturally occurring or synthetic antioxidants.[2] In order

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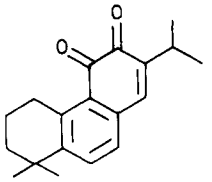


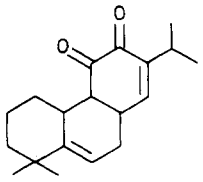
1

to confirm the structure and to give access to this and related compounds for antioxidant activity studies, we undertook the synthesis of 1. We report that 1 can be prepared in a single chemical operation from 3-isopropyl-o-benzoquinone (2) and 6,6-dimethyl-1-vinylcyclohexene (3, Scheme I).

Oxidation of commercially available[3] 3-isopropylcatechol to the orthoquinone 2 occurred rapidly upon treatment with lead tetracetate[4] and produced 2 as a red, viscous oil which showed no OH stretch in the IR spectrum. Because of the instability of 2, it was prepared only as needed and used immediately without purification. Other methods of oxidation, including cerium(IV) sulfate,[5] silver(I) oxide,[6] silver(II) oxide,[6] silver(I) carbonate on Celite,[7] and sodium metaperiodate[8] were much less successful. The second component, diene 3, was prepared from 2,2-dimethylcyclohexanone[9] by modifying the literature procedure.[10]

The Diels–Alder reaction[11] between 2 and 3 was studied at differing times and temperatures and with and without Lewis acid catalysis. The results are displayed in Table I. The most successful conditions (entry 4) involved a five-fold excess of 2 with 3 in ethanol for 6 h at reflux temperature. In this way 1 could be isolated by column chromatography in a reproduceable (six experiments) 28–30% yield. About 5% of 3 could also be recovered, but little or no 2 remained. Lower temperatures or longer reaction times proved detrimental. Lewis acid catalysis led to no 1 whatever, probably as the result of oligomerization of 2, since 3 was not consumed.

Neither the simple Diels–Alder adduct of 2 and 3 nor the catechol corresponding to 1 could be isolated, suggesting that under these conditions the primary adduct 4 is rapidly oxidized to 1 by excess 2. The alternative regioisomer 5 was likewise not isolated, although it might



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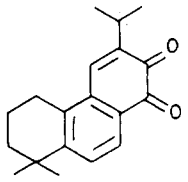

5

have been present in traces. Preference for 1 over 5 was predicted, since a directing alkyl group at the terminus of the diene partner is more influential in determining Diels–Alder regiochemistry than a similar group at an internal position.[12,13] Varying amounts of 3-isopropylcatechol and dimers of 2 were also present in the reaction mixture, as expected, but no other product could be isolated in pure form.

Scheme I

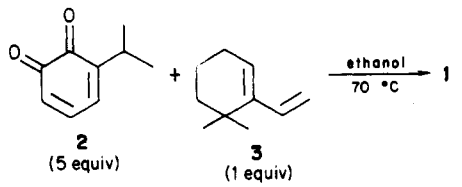

Table I. Diels–Alder Reaction of 2 and 3

entry	catalyst	solvent	time (h)	temp (°C)	% yield
1		EtOH	24	0	8
2		EtOH	12	25	12
3		EtOH	12	60	21
4		EtOH	6	78	28–30
5	$AlCl_3$	CH_2Cl_2	12	−78	0
6	$AlCl_3$	CH_2Cl_2	12	0	0
7	$EtAlCl_2$	CH_2Cl_2	12	−78	0
8	$EtAlCl_2$	CH_2Cl_2	12	0	0

The identity of synthetic 1 with material from the natural source was confirmed by TLC, mp, mmp, and 400-MHz ^1H NMR comparison. Rosmariquinone thus has the structure 1 as postulated, and quantities are now available by this route for the study of its antioxidant behavior.

Experimental Section

Apparatus and Reagents. Melting points were determined on an Electrothermal apparatus and are uncorrected. Infrared (IR) spectra were recorded by using a Perkin-Elmer Model 727B spectrophotometer (absorption maxima are in cm^{-1}). Proton nuclear magnetic resonance (NMR) spectra were obtained on deuteriochloroform solutions with a Varian XL-400 instrument. Chemical shifts are reported in parts per million downfield from tetramethylsilane and coupling constants are in hertz. Ultraviolet–visible spectra were obtained with a Hewlett-Packard 5451A diode array spectrophotometer.

Precoated silica gel plates (Baker Si250F) were used for analytical thin layer chromatography (TLC). E. Merck silica gel 60 (230–400 mesh) was employed for column chromatography. Tetrahydrofuran (THF) was distilled from benzophenone ketyl. Dichloromethane was distilled from calcium hydride. Other reagents were used as received from commercial suppliers. Organic solutions were dried over anhydrous sodium sulfate. All reactions were run under argon atmosphere. Distillations were performed bulb-to-bulb using a Büchi Kugelrohrofen.

6,6-Dimethyl-1-vinylcyclohexene (3). A 1 M solution of vinylmagnesium bromide in THF (12 mL) was cooled to −78 °C and a solution of 1 g (7.9 mmol) of 2,2-dimethylcyclohexanone in 10 mL of THF was added with stirring. After 2 h at −78 °C the mixture was warmed to 0 °C, quenched with saturated aqueous sodium bicarbonate (20 mL), and extracted with ether (3 × 25 mL). The combined extracts were dried, concentrated, and distilled (56 °C, 4 mm) to give 1.025 g (85%) of 2,2-dimethyl-1-vinylcyclohenanol.

A mixture of 200 mg (1.32 mmol) of 2,2-dimethyl-1-vinylcyclohexanol and 716 mg (5.26 mmol) of potassium bisulfate was heated at 150 °C for 10 min. Distillation (150 °C, 760 mm) gave 136 mg (76%) of 3: NMR 1.05 (s, 6 H), 1.4–1.9 (m, 4 H), 2.0–2.2

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(m, 2 H), 4.91 (br t, J = 8, 1 H), 5.25 (br d, J = 18, 1 H), 5.74–5.78 (m, 1 H), 6.28 (br dd, J = 12, 18, 1 H).

3-Isopropyl-*o*-benzoquinone (2). A solution of 3-isopropylcatechol (152 mg, 1 mmol) in 15 mL of dichloromethane was treated with a solution of 886 mg (2 mmol) of lead tetraacetate in 5 mL of dichloromethane and the mixture was stirred for 5 min at 23° C and then filtered. The resulting organic solution was washed with dilute aqueous hydrochloric acid, dilute aqueous sodium bicarbonate, and water and then dried and concentrated to give 150 mg (100% crude yield) of **2** as a red, viscous oil: NMR 1.10 (d, J = 6.7, 6 H), 2.95 (septet, J = 7, 1 H), 6.27 (dd, J = 10, 1.2, 1 H), 6.70 (dd, J = 1.2, 6, 1 H), 7.02 (dd, J = 10, 6.4, 1 H).

Rosmariquinone (1). A mixture of 50 mg (0.37 mmol) of **3**, 277 mg (1.85 mmol) of freshly prepared **2**, and 25 mL of absolute ethanol was heated under reflux for 6 h, at which point TLC indicated no increase in product formation. The reaction mixture was concentrated and subjected to column chromatography using 3:97 ethyl ether/petroleum ether as eluant. The product corresponding to TLC R_f 0.30 (5:95 ether/petroleum ether) was collected as a red solid (31 mg, 30%), mp 92–94 °C. One crystallization from hexane raised the melting point to 94–95 °C. An authentic sample of **1** melted at 96–96.5 °C, with mmp 94–95 °C: UV–vis (ethanol) λ_{max} 230 (15 750), 260 (19 000), 370 (2000), 480 (2250).

Acknowledgment. We are grateful to Prof. C.-T. Ho of the Department of Food Science, Rutgers University, for providing the authentic sample of **1** and a preprint of ref 1 and to Rutgers University for research support through the BRSG program.

Registry No. 1, 27210-57-7; 2, 98353-93-6; 3, 18238-29-4; 2,2-dimethylcyclohexanone, 1193-47-1; 2,2-dimethyl-1-vinylcyclohexanol, 18238-28-3; 3-isopropylcatechol, 2138-48-9.

Direct Nucleophilic Attack on Sulfur Atom of a Norbornadienyl Sulfone

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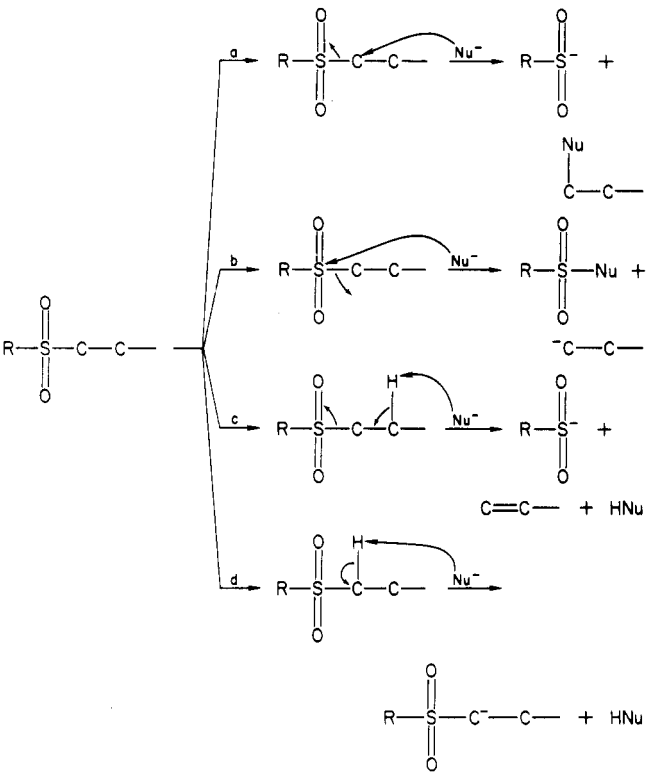
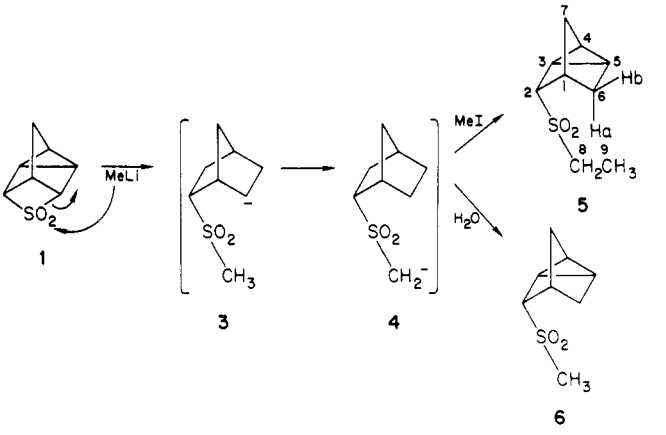
The mode of the reaction of a sulfone with a nucleophilic base is sometimes not easy to predict since sulfone itself is a electron-withdrawing group which can activate α-carbons to become nucleophilic. On the other hand, sulfinate is a moderately good leaving group which caused its α-carbons suitable for nucleophilic substitution. In addition, the strong electronegativity of the oxygens on the sulfone causes the sulfur atom to be a highly electrophilic center. When a sulfone system is treated with a nucleophile or a base, four reaction pathways may take place (Scheme I).

Deprotonation reactions of sulfones via pathway c and pathway d are most frequently observed. Reactions involving the nucleophilic attack at the α-carbon which knocks out a sulfinate (pathway a) have been observed.[2] Very recently, it was shown that this pathway was highly synthetically useful by way of Lewis acid catalyzed Friedel–Crafts alkylation reactions.[3] Reactions by pathway b were reported only in the cases where the leaving groups were moderately stabilized or in systems where no other

Scheme I



Scheme II



electrophilic centers existed.[4] In other words, nucleophilic bases would normally act more like bases than like nucleophiles in reactions with sulfones. The steric crowdedness of the sulfone function should be responsible for these observations. However, nucleophilic substitution reactions by pathways a and b were expected to occur more easily if the steric accessibility could be enhanced. Norbornadienyl sulfone **1**, with its sulfone function in a strained four-membered ring, was found to be a good example for nucleophilic attack.

When a nonnucleophilic base, such as NaH or lithium hexamethyldisilazide (LiHMDS), was treated with **1** followed by alkylation with MeI under various conditions, the starting material was completely recovered, giving a signal of the weak acidity of the α-positions and a good

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