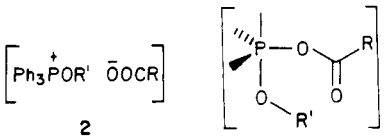
ester (entry 10, Table I) prepared from (−)-2-octanol and potassium benzoate;[17] under present reaction conditions $[\alpha]^{22}_D$ (c 0.013 g/mL, $CHCl_3$) was +3.8°. The possibility of partial or double inversion via an intermediate alkyl chloride has been eliminated since ethyl 2-chloropropionate in carbon tetrachloride with potassium benzoate did not produce any significant amounts of the corresponding ester. A carbonium ion mechanism was considered to be unreasonable due to the nonpolar nature of the reaction medium and also due to the observed inversion with racemization. Also ruled out is the possibility of carboxylic acid activation[20] mechanism because the observed product does not retain the configuration.

Although a definitive mechanism awaits further study, the esterification is assumed to proceed initially via 1 and then 2, which could either be a tight ion pair[9] or a pentacoordinate species such as 3 in which the carboxylate group is either equatorial or apical.[18,19] This species, via



2 3

a four-atom or six-atom cyclic transition state (concerted or nonconcerted fashion), could lead to either retention or inversion, respectively. Molecular models appear to indicate the latter possibility is preferential if not exclusive. However, the tight ion pair mechanism, which is well accepted with oxyphosphonium salts, cannot be excluded.

In analogy to the Mitsunobu and related reactions, (alcohol activation), other heteroatom nucleophiles, e.g., N and O react in a similar manner to give amines and ethers.[21–23] However, sulfur nucleophiles such as potassium salt of ethylxanthic acid did not give desired product.

Experimental Section

IR spectra were obtained on a Perkin-Elmer 598 infrared spectrometer using either thin films or Nujol mulls on NaCl plates. NMR spectra were obtained on an EM360A spectrometer with $CDCl_3$ as the solvent and tetramethylsilane as an internal standard. Analytical and preparative TLC were performed with silica plates from Analtech. All reagents were used as received. Aldrich's IR and NMR spectra were referred to when available and others were obtained from authentic samples prepared by literature procedures.

Preparation of Benzyl Acetate. Potassium acetate (0.20 g), carbon tetrachloride (0.76 g), triphenylphosphine (0.588 g), and benzyl alcohol (0.21 g) were placed in a round-bottomed flask fitted with an efficient water condenser and the semisolid mixture was heated at 55–60 °C for 4 h with stirring. The solvent ($CHCl_3$ and excess CCl_4) was then removed on a rotary evaporator and 10 mL of hexane was added; the mixture was stirred for 15 min and then filtered. The hexane solution was concentrated to give an oil, which was then distilled (Kugelrohr) under reduced pressure [110 °C (2 mm)] to give 0.18 g of benzyl acetate, 60% yield.

Preparation of 4-[(Benzoyloxy)methyl]-1,3-dioxolan-2-one. Triphenylphosphine (0.55 g), carbon tetrachloride (0.91 g), glycerol carbonate (0.24 g), and potassium benzoate (0.35 g) were heated with stirring at 55–60 °C for 5.5 h. During this period, the reaction mixture underwent solidification. After the reaction was complete, the residue was dissolved in chloroform and filtered to remove potassium chloride. The solvent from the filtrate was removed, and the residue was dissolved in a small amount of chloroform and then chromatographed over silica gel with hexane/ether (95:5) to give 0.28 g of the dioxolanone: 68% yield; mp 68–69 °C; NMR ($CDCl_3$) δ 4.5 (4 H), 5.05 (1 H), 7.3 (3 H), 8.05 (2 H).

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Registry No. PhCOOK, 582-25-2; H_3CCOOK, 127-08-2; PhCH=CHCOOK, 16089-48-8; 4-$O_2NC_6H_4COOK$, 15922-01-7; $PhCOOCH_2CH_3$, 93-89-0; $PhCOOCH_2Ph$, 120-51-4; $PhCOOCH_2CH{=}CH_2$, 583-04-0; $PhCOO(CH_2)_2Si(CH_3)_3$, 98760-24-8; (±)-$PhCOOCH(CH_3)COOCH_2CH_3$, 1020-09-3; (±)-$PhCOOCH(CH_3)CN$, 98777-16-3; (±)-$PhCOOCH(CH_3)(CH_2)_5CH_3$, 98819-31-9; CH_3COOCH_2Ph, 140-11-4; $PhCH{=}CHCOOCH_2CH_3$, 103-36-6; 4-$O_2NC_6H_4COOCH(CH_3)_2$, 13756-40-6; $(CH_3)_3Si(CH_2)_2OH$, 2916-68-9; (−)-$CH_3CH(OH)COOCH_2CH_3$, 7699-00-5; (±)-$CH_3CH(OH)CN$, 42492-95-5; (−)-$CH_3(CH_2)_5CH(CH_3)OH$, 5978-70-1; $CH_2{=}C(CH_3)CH_2OH$, 513-42-8; $CCl_2{=}C(Cl)CH_2OH$, 3266-39-5; $ClCH_2CH_2OH$, 107-07-3; Ph_3P, 603-35-0; CCl_4, 56-23-5; 4-pyridinecarboxylic acid potassium salt, 25108-37-6; (±)-oxiranylmethyl benzoate, 98760-25-9; (±)-[(benzoyloxy)methyl]-1,3-dioxolan-2-one, 98760-26-0; (±)-4-[(benzoyloxy)methyl]-2,2-dimethyl-1,3-dioxolane, 98760-27-1; methyl 4-pyridinecarboxylate, 2459-09-8; benzyl 4-pyridinecarboxylate, 21182-01-4; (±)-oxiranemethanol, 61915-27-3; (±)-4-(hydroxymethyl)-1,3-dioxolan-2-one, 63121-19-7; (±)-4-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolane, 22323-83-7; Pen-G allyl ester, 80127-23-7; Pen-G 2-methylallyl ester, 65590-78-5; Pen-G 2,3,3-trichloro-2-propenyl ester, 98760-28-2; Pen-G 2-chloroethyl ester, 98760-29-3; Pen-G benzyl ester, 1254-56-4; Pen-G potassium salt, 113-98-4.

(17) Complete inversion $[\alpha]^{22}_D$ is +34.4°.[8]
(18) Weiss, R. G.; Snyder, E. I. *J. Org. Chem.* **1970**, *35*, 1627.
(19) Weiss, R. G.; Snyder, E. I. *J. Org. Chem.* **1971**, *36*, 403.
(20) One of the reviewers suggested to include this alternate reaction pathway to explain the lack of stereocontrol.
(21) E.g., with present procedure, methyl lactate was reacted with potassium 2,6-dichlorophenoxide to give methyl 2-(2,6-dichlorophenoxy) propionate in 80% yield. Similarly reacted potassium phthalimide.
(22) Miller, M. J.; Mattingly, P. G.; Morrison, M. A.; Kerwin, J. F., Jr. *J. Am. Chem. Soc.* **1980**, *102*, 7026.
(23) Garcia, J.; Urpi, F.; Vilarrasa, J. *Tetrahedron Lett.* **1984**, 4841.

Acetylative Cleavage of (Arylsulfonyl)ureas to *N*-Acetylarenesulfonamides and Isocyanates

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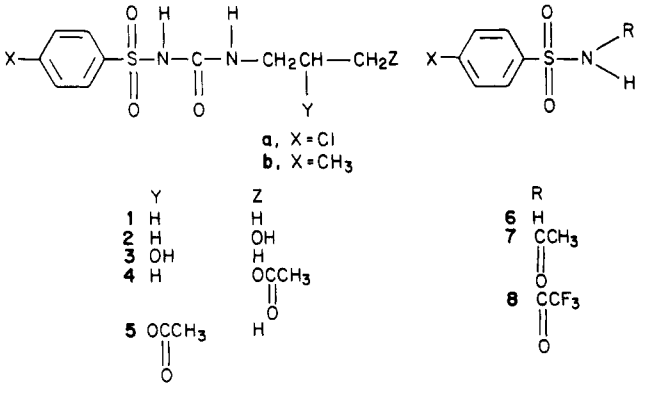
Oral hypoglycemic agents of the class exemplified by 1-[(4-chlorophenyl)sulfonyl]-3-(*n*-propyl)urea (chlorpropamide, **1a**) are known to be metabolized by man[1] and rodents[2] by hydroxylation on the aliphatic side chain. In



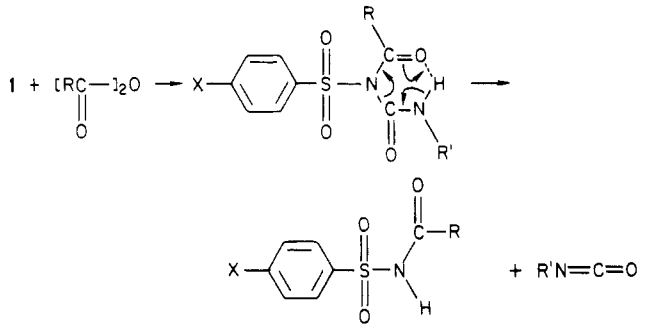
a, X = Cl
b, X = CH_3

	Y	Z
1	H	H
2	H	OH
3	OH	H
4	H	$OCCH_3$ (O)
5	$OCCH_3$ (O)	H

	R
6	H
7	CCH_3 (O)
8	CCF_3 (O)

(1) Taylor, J. A. *Clin. Pharmacol. Ther. (St. Louis)* **1972**, *13*, 710.

Scheme I



our attempts to prepare acetate derivatives of these hydroxylated metabolites of **1a** for biological studies,[3] the 3′-hydroxyl derivative **2a** was reacted with excess Ac_2O in pyridine at room temperature. However, the expected ester **4a** was not obtained; instead, the *N*-acetylated sulfonamide **7a** was isolated in 71% yield. Under the same conditions, the 2′-hydroxyl derivative **3a** gave 7a in 83% yield.

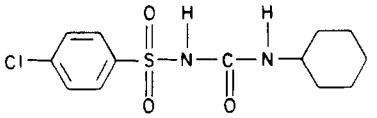
Since the hydroxylated derivatives **2a** and **3a** are known to be unstable in acid and to give rise to **6a** by facile cleavage of the side chain,[2a] it was thought that **7a** might have been produced from **2a** and **3a** via **6a** under the conditions of the acetylation reaction. However, acetylation of chlorpropamide (**1a**) itself produced **7a**, indicating that the presence of side chain hydroxyl groups was not obligatory for acetylative cleavage.

Analogous results were obtained when 1-(*p*-tolylsulfonyl)-3-(*n*-propyl)urea (**1b**) or its side chain hydroxylated derivatives **2b** and **3b** were acetylated under the same conditions. Thus, *N*-acetyl-*p*-toluenesulfonamide (**7b**) was the only isolable product from the acetylation of **1b**, **2b**, or **3b**. In order to obtain the acetates **4a**, **4b**, **5a**, and **5b**—albeit in poor yields—it was necessary to use THF as solvent/diluent with only a slight excess of Ac_2O. Even under these conditions, the intrinsic formation of **7a** and **7b** required chromatography of the reaction mixture to effect purification of the acetates.

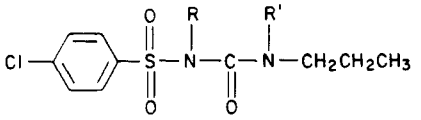
The acylation of **1a** could be followed by ^1H NMR spectrometry in $CDCl_3$ by using trifluoroacetic anhydride, an acylating agent which is transparent in this system. Concommitant to the disappearance of an N–H triplet at δ 6.47, the multiplet centered at δ 3.13 (due to the methylene protons adjacent to the urea nitrogen) shifted to lower field such that their chemical shifts now coincided with the corresponding methylene protons of *n*-propyl isocyanate. The aromatic protons also shifted to lower field, and the A_2B_2 pattern became superimposable with the spectrum of **8a**.[4] Indeed, **8a** was isolated in 94% yield from a reaction mixture scaled up for this purpose. Likewise, the formation of **7a** was detected by ^1H NMR spectroscopy in the reaction of acetic anhydride with **1a** in the presence of pyridine-d_5 except that heating was required, and this cleavage product was isolated in preparative scale reactions.

The NMR spectrum of a 1:1 synthetic mixture of **7a** and *n*-propyl isocyanate with added pyridine-d_5 did not change even after standing overnight at room temperature. In a separate experiment, **7a** remained unchanged (by TLC) when heated under reflux overnight with 5-fold excess of *n*-propyl isocyanate in acetonitrile, indicating that the reverse, condensation reaction does not take place under these conditions.

Acetylation of the sodium salt of chlorcyclohexamide (**9**) with acetyl chloride gave rise again to **7a** as well as to cyclohexyl isocyanate. The latter was detected by a characteristic isocyanate peak at 2230 cm^{-1} in its IR spectrum and was isolated by conversion to dicyclohexylurea by reaction with cyclohexylamine.



9



10, R=H; R′=CH_3
11, R=$COCH_3$; R′=CH_3
12, R=CH_3; R′=H
13, R=CH_3; R′=$COCF_3$

We envision this acetylative cleavage of the (arylsulfonyl)ureas to proceed by initial acylation of the sulfonamide N^1 nitrogen followed by elimination of an alkylisocyanate as depicted in Scheme I. This reaction formally resembles the reaction of (arysulfonyl)ureas with phosgene, which gives rise to arenesufonyl isocyanates and the corresponding side chain derived alkyl isocyanates.[5]

That the sulfonamide N^1 nitrogen is more reactive than the N^3 urea nitrogen is supported by the observation that the N^3-methyl derivative **10** was readily acetylated with acetyl chloride/triethylamine to the stable **11**, whereas the isomeric **12** was resistant to acetylation under these conditions.[6] Methylation of **1** is also known to take place exclusively on the acidic N^1 nitrogen.[6,7]

Although **7a** has not been detected as a urinary metabolite of **1a** in rodents or in man, the deacetylated **6a**—purported to be derived from a metabolite of **1a** during the workup of the urine—has been found.[2b] Since arenesulfonamides are readily acetylated on the sulfonamide nitrogen in vivo,[8,9] it is tempting to speculate whether the acetylative cleavage reaction of (arylsulfonyl)ureas described here (Scheme I) might not also be mimicked in a metabolic process occurring in vivo. The liberation of highly reactive alkyl isocyanates in this process could result in adverse pharmacological side effects such as enzyme inhibition.

Experimental Section

Melting points were determined on a Fischer-Johns melting point apparatus and are corrected to reference standards. ^1H NMR spectra were recorded on a Varian T-60A nuclear magnetic resonance spectrometer using tetramethylsilane (Me_4Si) as internal standard. IR spectra were taken as KBr pellets or in CH_2Cl_2 on

(2) (a) Thomas, R. C.; Judy, R. W. *J. Med. Chem.* **1972**, *15*, 964. (b) Taylor, J. A. *Drug Metab. Dispos.* **1974**, *2*, 221.
(3) Nagasawa, H. T.; DeMaster, E. G.; Kwon, C.-H.; Fraser, P. S.; Shirota, F. N. *Alcohol* **1985**, *2*, 123.
(4) Although not further elaborated here, entirely analogous results were obtained with tolbutamide.
(5) Ulrich, H. R.; Tucker, B.; Sayigh, A. A. R. *J. Org. Chem.* **1966**, *31*, 2658.
(6) However, *trifluoroacetylation* of the latter to **13** under more vigorous conditions is possible, and, in fact, this reaction has been used for derivatization in the gas chromatogrphic analysis of **1a** and other sulfonylureas. Brasselton, W. E., Jr.; Bransome, E. D., Jr.; Ashline, A. C.; Stewart, J. T.; Honigberg, I. L. *Anal. Chem.* **1976**, *48*, 1386.
(7) (a) Sabih, K.; Sabih, K. *J. Pharm. Sci.* **1970**, *59*, 782. (b) Midha, K. K.; Awang, D. V. C.; McGilveray, I. J.; Kleber, J. *Biomed. Mass Spectrom.* **1976**, *3*, 100.
(8) Shirota, F. N.; Nagasawa, H. T.; Kwon, C.-H., Demaster, E. G. *Fed. Proc.* **1984**, *43*, 347.
(9) Boyer, F.; Saviard, M.; Dechavassine, M. *Ann. Inst. Pasteur, Paris* **1956**, *90*, 339.

a Beckman IR-10 infrared spectrophotometer. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. Research-grade chlorpropamide (**1a**) was kindly supplied by Pfizer, Inc., but was also prepared in larger quantities with a general procedure.[10] 4-Chlorobenzenesulfonyl isocyanate was purchased from Morton Thiokol, Inc. The acetylative cleavage reactions and chromatography effluents were monitored by TLC on silica gel GF (Analtech) using the solvent systems indicated.

1-(*p*-Tolylsulfonyl)-3-(*n*-propyl)urea (1b) was prepared from *p*-toluenesulfonamide and *n*-propyl isocyanate by using the general procedure described for the preparation of deuterated tolbutamide[10] and recrystallized from EtOH/H_2O; mp 151–153 °C (lit.[11] mp 151–152 °C).

1-[(4-Chlorophenyl)sulfonyl]-3-(3-hydroxypropyl)urea (2a). This compound was prepared as described below for **2b** except that 4-chlorobenzenesulfonyl isocyanate was substituted for *p*-toluenesulfonyl isocyanate. The crude product was recrystallized from EtOAc to give **2a** in 50% yield as colorless crystals: mp 123–124.5 °C; ^{1}H NMR (CD_3COCD_3 + D_2O) δ 7.63 (A_2B_2, q, 4 H, J = 9 Hz, $\Delta\nu_{AB}$ = 22 Hz, Ar H), 3.30 (*t*, 2 H, J = 6 Hz, CH_2CH_2OH), 2.97 (*t*, 2 H, J = 6 Hz, $NHCH_2CH_2$), 2.22 (*m*, 2 H, $CH_2CH_2CH_2$). Anal. Calcd for $C_{10}H_{13}ClN_2O_4S$: C, 41.03; H, 4.48; N, 9.57. Found: C, 41.07; H, 4.53; N, 9.32.

1-(*p*-Tolylsulfonyl)-3-(3-hydroxypropyl)urea (2b). 3-Aminopropan-1-ol (7.8 mL, 0.10 mol) was silylated with bis(trimethylsilyl)acetamide (24.6 mL, 0.10 mol) in 50 mL of dry THF for 30 min. The reaction mixture was then evaporated to incipient dryness on a rotating evaporator, the residue dissolved in 100 mL of hexane, and the solution filtered. To the stirred filtrate was added *p*-toluenesulfonyl isocyanate[5] (3.94 g, 0.020 mol) in 50 mL of dry THF dropwise over 30 min at ice bath temperature. After 15 min at room temperature, the solvent was evaporated in vacuo and the thick liquid residues was dissolved in 100 mL of H_2O by stirring. The aqueous solution was then extracted with EtOAc (2 × 100 mL). The separated aqueous layer was acidified to pH 3 with 2 N HCl and then extracted with EtOAc (3 × 60 mL). The combined EtOAc extract was dried (Na_2SO_4), and the solvent was evaporated in vacuo to yield 5.3 g of a clear oil. A portion (2.0 g) of the product was applied to a silica gel column (2.5 × 20 cm, E. Merck, 230–400 mesh) and eluted with EtOAc at 20 psi. The desired fractions containing product were pooled and evaporated in vacuo to give 0.70 g of solids, which were crystallized from EtOAc/hexane to give 0.60 g of crystalline **2b**: mp 107–108 °C; ^{1}H NMR (CD_3OD) δ 7.59 (A_2B_2, q, 4 H, J = 8 Hz, $\Delta\nu_{AB}$ = 30 Hz, Ar H), 3.52 (t, 2 H, J = 6 Hz, CH_2OH), 3.16 (m, 2 H, $NHCH_2$), 2.43 (s, 3 H, Ar CH_2), 1.69 (m, 3 H, $CH_2CH_2CH_2$). Anal. Calcd for $C_{11}H_{16}N_2O_4S$: C, 48,52; H, 5.92; N, 10.29. Found: C, 48.36; H, 5.74; N, 10.16.

1-[(4-Chlorophenyl)sulfonyl]-3-(2-hydroxypropyl)urea (3a). Prepared essentially as described for compound **2a**, except that 1-aminopropan-2-ol was coupled with 4-chlorobenzenesulfonyl isocyanate. No attempt was made to optimize the yield of **3a** (30%): mp 127.5–129 °C; ^{1}H NMR (CD_3COCD_3 + D_2O) δ 7.56 (A_2B_2, q, 4 H, J = 9 Hz, $\Delta\nu_{AB}$ = 22 Hz, Ar H), 3.92 (m, 2 H, CH_2CHCH_3), 3.12 (fused d, 2 H, $NHCH_2CH$), 1.20 (d, 3 H, J = 7 Hz, $CHCH_3$). Anal. Calcd for $C_{10}H_{13}ClN_2O_4S$: C, 41.03; H, 4.48; N, 9.57. Found: C, 40.88; H, 4.54; N, 9.50.

1-(*p*-Tolylsulfonyl)-3-(2-hydroxypropyl)urea (3b). *p*-Toluenesulfonyl isocyanate (5.92 g, 0.030 mol) in 100 mL of dry 1,4-dioxane was added dropwise over 30 min to 1-aminopropan-2-ol (3.76 g, 0.50 mol) in 400 mL of dry 1,4-dioxane at <0 °C with vigorous stirring under a nitrogen atmosphere. After an additional hour, the solvent was removed in vacuo, and the residual liquid was dissolved in 150 mL of H_2O. The solution was then extracted with EtOAc (2 × 100 mL), and the separated aqueous layer was acidified with 6 N HCl to pH 2.5. After extraction again with EtOAc (2 × 100 mL), the combined EtOAc extract was dried (Na_2SO_4) and the solvent removed to give crude **3b**. Recrystallization from THF/EtOAc/hexane gave 7.85 g (96.1% yield) of pure **3b**: mp 134–135 °C; ^{1}H NMR (CD_3OD) δ 7.63 (A_2B_2 q, 4 H, J = 8 Hz, $\Delta\nu_{AB}$ = 29 Hz, Ar H), 3.75 (m, 1 H, CH_2CHCH_3), 3.61 (m, 2 H, $NHCH_2$), 2.48 (s, 3 H, $CH_3C_6H_4$), 1.10 (d, 3 H, J = 6 Hz, CH_3CH). Anal. Calcd for $C_{11}H_{16}N_2O_4S$: C, 48.52; H, 5.92; N, 10.29. Found: C, 48.42, H, 5.93; N, 10.39.

Acetylative Cleavage of 1a, 2a, and 3a to 7a. 1-[(4-Chlorophenyl)sulfonyl]-3-(*n*-propyl)urea (**1a**, 1.38 g, 5.00 mmol) was stirred with acetic anhydride (2.55 g, 2.36 mL, 25.0 mmol) in 30 mL of pyridine at room temperature overnight. The reaction mixture was diluted with 30 mL of H_2O and then acidified to pH 2 with 6 N HCl at ice bath temperature. After extraction with EtOAc (3 × 50 mL), the EtOAc extract was dried (Na_2SO_4), and the solvent was evaporated in vacuo. The residual solids were recrystallized from methanol to give 0.64 g (54.8% yield) of crystalline *N*-acetyl-*p*-chlorobenzenesulfonamide (**7a**): mp 194.5–195.5 °C (lit.[12] mp 191–192 °C); ^{1}H NMR ($CDCl_3$ + CD_3OD) δ 7.72 (A_2B_2, q, 4 H, J = 9 Hz, $\Delta\nu_{AB}$ = 29 Hz, Ar H), 2.03 (s, 3 H, $CH_3C{=}O$). This product was identical with respect to mp, TLC mobility, and ^{1}H NMR and IR spectra with an authentic sample of **7a**. When **2a** and **3a** were treated in the same manner as described above, **7a** was obtained in 71.1% and 83.0% yields, respectively.

Acetylative Cleavage of 1b, 2b, and 3b to 7b. 1-(*p*-Tolylsulfonyl)-3-(*n*-propyl)urea (**1b**, 1.28 g, 5.00 mmol) was treated as described above for the acetylation of **1a**. The crude product was recrystallized from MeOH/H_2O to give 1.05 g (98.5% yield) of crystalline *N*-acetyl-*p*-toluenesulfonamide (**7b**): mp 138–139 °C [lit.[13] mp 139 °C]. The ^{1}H NMR and IR spectra of this product were identical with those of an authentic sample of **7b** prepared by acetylation of **6b**. Similarly, **2b** and **3b**, when treated in identical manner as described above, gave **7b** in 75.0% and 65.6% yields, respectively.

1-[(4-Chlorophenyl)sulfonyl]-3-(3-acetoxypropyl)urea (4a). Compound **2a** (1.80 g, 6.10 mmol) in 40 mL of THF and 10 mL of pyridine was allowed to react with acetic anhydride (0.87 g, 8.5 mmol) at room temperature overnight. After removal of the solvent in vacuo, the residual liquid was dissolved in 50 mL of H_2O and the aqueous solution acidified to pH 2 with 6 N HCl. The mixture was then extracted with EtOAc (3 × 50 mL), and the EtOAc extract was evaporated in vacuo. The thick liquid residue was applied to a silica gel column (30 g, 35–70 mesh) and eluted with EtOAc/hexane/AcOH (50:100:1). The fractions containing product were pooled and evaporated in vacuo to give a semisolid residue, which was crystallized from EtOAc/hexane to give 0.68 g (33% yield) of **4a** as colorless crystals: mp 139.5–141 °C; ^{1}H NMR ($CDCl_3$) δ 7.70 (A_2B_2, q, 4 H, J = 9 Hz, $\Delta\nu_{AB}$ = 20 Hz, Ar H), 6.70 (br m, 1 H, NH), 4.15 (t, 2 H, J = 6 Hz, CH_2CH_2O), 3.35 (q, 2 H, J = 7 Hz, $NHCH_2CH_2$), 2.15 (s, 3 H, $CH_3C{=}O$), 1.87 (m, 2 H, $CH_2CH_2CH_2$). Anal. Calcd for $C_{12}H_{15}N_2ClO_5S$: C, 43.05; H, 4.52; N, 8.37. Found: C, 42.80; H, 4.64; N, 8.28.

1-(*p*-Tolylsulfonyl)-3-(3-acetoxypropyl)urea (4b). This compound was prepared as described above for **4a** except that **2b** was substituted for **2a**. The crude product, a thick liquid, was flash chromatographed on a silica gel column (2.5 × 20 cm, 230–400 mesh) using EtOAc/hexane/AcOH (1000:1000:1) as eluent at 20 psi to give, after recrystallization from MeOH/H_2O, 0.28 g (30% yield) of crystalline *4b*: mp 123–125 °C; ^{1}H NMR ($CDCl_3$) δ 7.53 (A_2B_2, q, 4 H, J = 8 Hz, $\Delta\nu_{AB}$ = 27 Hz, Ar H), 6.70 (m, 1 H, NH), 4.07 (t, 2 H, J = 6 Hz, CH_2CH_2O), 3.30 (q, 2 H, J = 6 Hz, CH_2NH), 2.43 (s, 3 H, $CH_3C_6H_4$), 2.08 (s, 3 H, $CH_3C{=}O$), 1.82 (m, 2 H, $CH_2CH_2CH_2$). Anal. Calcd for $C_{13}H_{18}N_2O_5S$: C, 49.67; H, 5.77; N, 8.91. Found: C, 49.53; H, 5.91; N, 8.79.

1-[(4-Chlorophenyl)sulfonyl]-3-(2-acetoxypropyl)urea (5a). This compound was prepared essentially as described for the preparation of **4a** except that **3a** was the starting material. After flash chromatography, the product was recrystallized from Et_2O/hexane: mp 141–143 °C; 12% yield; ^{1}H NMR ($CDCl_3$) δ 7.67 (A_2B_2, q, 4 H, J = 8 H, $\Delta\nu_{AB}$ = 23 Hz, Ar H), 4.93 (m, 1 H, CH_2CHCH_3), 3.37 (m, 2 H, $NHCH_2CH_2$), 2.05 (s, 3 H, $CH_3C{=}O$), 1.17 (d, 3 H, J = 6 Hz, CH_2CH_3). Anal. Calcd for $C_{12}H_{15}N_2ClO_5S$: C, 43.05; H, 4.52; N, 8.37. Found: C, 42.92; H, 4.60; N, 8.07. **7a** was also isolated from the early chromatographic fractions.

1-(*p*-Tolylsulfonyl)-3-(2-acetoxypropyl)urea (5b). The reaction conditions described for the preparation of **4b** were used

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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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