After stirring the golden yellow solution at 25 °C for 2h, it was cooled to −78 °C followed by the dropwise addition (5 min) of a solution of 5.4 mL (50 mmol) of 1-bromo-3-chloropropane in 5 mL of THF. The solution was allowed to warm to 25 °C overnight. The reaction mixture was poured into hexane and washed with 5% aqueous $NaHCO_3$ solution and twice with water, and the combined washes were backwashed with hexane. The combined hexane extracts were washed with saturated brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was distilled to yield 3.89 g (54%) of **3e** as a colorless liquid (GLC pure): bp 51–53 °C (0.2 mm) [lit.[3k] bp 43–44 °C (0.1 mm)]; NMR ($CDCl_3$) δ 1.76 (3 H, d, J = 7 Hz), 2.87 (4 H, m), and 6.00 (1 H, q, J = 7 Hz).

α,α-Bis(thioethyl)methylidenecyclohexane (3f) (Entry 11). To a solution of 1.87 mL (2.3 M, 4.3 mmol) of n-BuLi in 5 mL of THF at −78 °C maintained under an atmosphere of N_2 was added 1.2 mL (8.0 mmol) of N,N,N',N'-tetramethylethylenediamine followed by a solution of 0.32 g (2 mmol) of cyclohexanecarbodithioic acid (**1c**) in 1 mL of THF. The reaction mixture was maintained at −78 °C for 4 h, after which time 0.35 mL (4.3 mmol) of ethyl iodide was added to the orange solution, giving an immediate yellow-white suspension. After warming to 25 °C over 7 h, water was added and the mixture was thoroughly extracted with ether and backwashed with 5% aqueous $NaHCO_3$, water, and brine. The ethereal extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo, affording 0.48 g of crude yellow liquid: GLC, 71% yield (internal standard); NMR ($CDCl_3$) δ 1.16 (6 H, t, J = 6 Hz), 1.36–1.68 (6 H, m), and 2.49–2.87 (8 H, m).[7]

2,8-Bis(cyclohexylidene)-1,3,7,9-tetrathiacyclododecane (4). To a solution of 6.6 mmol of LDA (vide supra) in 8 mL of dry THF maintained under N_2 at 0 °C was added dropwise 1.56 mL (9.0 mmol) of dry HMPA followed by the dropwise addition of a solution of 0.48 g (3.0 mmol) of cyclohexanecarbodithioic acid (**1c**) in 1 mL of THF. The ice bath was removed, and the reaction mixture was allowed to warm to 25 °C over 1.5 h. The orange suspension was cooled to −78 °C (acetone–CO_2) followed by the dropwise addition of 0.34 mL (3.3 mmol) of freshly distilled 1-bromo-3-chloropropane. The reaction mixture was allowed to warm to 25 °C over a period of 6 h by allowing the CO_2 to evaporate. The reaction mixture was taken up in 50% benzene–hexane, washed successively with water, 5% aqueous sodium bicarbonate, water, and saturated brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to give an orange-brown solid. The residue was chromatographed on SiO_2 (25 g), providing (15% benzene–hexane) 171 mg (28.5% yield) of white crystals of dimer **4** (mp 128 °C). Recrystallization from absolute ethanol provided 101.2 mg of **4**: mp 129.5 °C; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.57 (12 H, m), 1.94 (4 H, quintet, J = 6.6 Hz), 2.62 (8 H, m), 3.01 (8 H, t, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 20 MHz) δ (relative intensity) 26.48 (45), 28.03 (100)[8] 32.92 (91), 34.20 (90), 121.21 (23), 154.00 (22); mass spectrum (70 eV), m/e 400 (M^+).

Anal. Calcd for $C_{20}H_{32}S_4$: C, 59.94; H, 8.05; S, 32.00. Found: C, 59.75; H, 8.07; S, 31.88.

The monomer **3g,** prepared by the modified method of adding the dianion and the dihalide simultaneously and slowly to THF at 25 °C (51% yield), had the following physical and spectral properties: mp 93.5 °C (lit. mp 92–93[3k] and 93.6–94 °C[3m]); ^1H NMR ($CDCl_3$, 90 MHz) δ 1.45–1.70 (6 H, m), 2.05–2.30 (2 H, m), 2.38–2.60 (4 H, m), 2.82–2.96 (4 H, m); ^{13}C NMR ($CDCl_3$, 20 MHz) δ (relative intensity) 25.16 (46), 26.38 (32), 27.40 (87), 30.25 (77), 31.99 (100), 115.59 (10), 144.87 (14); mass spectrum (70 eV), m/e 200 (M^+).

Anal. Calcd for $C_{10}H_{16}S_2$: C, 59.94; H, 8.05; S, 32.00. Found: C, 59.94; H, 8.06; S, 31.99.

Acknowledgment. The financial support of the National Institutes of Health (CA-08869) and Hoffmann-La Roche (Nutley) is greatly appreciated. The Bruker HX-270 NMR instrument is supported by the National Institutes of Health Research Grant No. 1-PO7-PR00798 from the Division of Research Sources.

Registry No.—**1a,** 594-03-6; **1b,** 1892-30-4; **1c,** 35329-08-9; **3a,** 4992-59-0; **3b,** 21777-31-1; **3c,** 6251-15-6; **3d,** 13879-93-1; **3e,** 51102-62-6; **3f,** 66483-12-3; **3g,** 37891-71-7; **4,** 66483-11-2.

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(7) Identical with the product of entry 10. Anal. Calcd for $C_{11}H_{20}S_2$: C, 61.05; H, 9.32; S, 29.63. Found: C, 60.79; H, 9.29; S, 29.47.
(8) A ^{13}C spectrum at 68 MHz resolved this signal into two peaks: δ 28.12 (97) and 27.92 (60).

Synthesis and Oxidation of Substituted *N*-Phenyl-2-[(phenylamino)sulfinyl]acetamides

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N-Phenyl-2-[(phenylamino)sulfinyl]acetamide (**4a**) was first prepared in our laboratory by the reaction of aniline with the adduct formed from ketene and sulfur dioxide.[1] We also reported the cycloaddition of ketene (**1**) and *N*-sulfinylaniline (**2**) to give *N*-phenyl-1,2-thiazetidin-3-one 1-oxide (**3**) and described the reactions of **3** with aniline and *p*-toluidine to afford the corresponding *N*-phenyl-2-[(phenylamino)sulfinyl]acetamides, **4a** and **4b,** respectively.[2]

The present communication describes a more convenient synthesis of **3** and provides experimental details regarding the facile cleavage of **3** with substituted anilines and the oxidation of the resultant sulfinamides **4** to the corresponding sulfonamides **5.**

Treatment of approximately 1.5 mol equiv of gaseous ketene **1** with 1 equiv of *N*-sulfinylaniline (**2**) in acetone at −78 °C for 2 h was found to give *N*-phenyl-1,2-thiazetidin-3-one 1-oxide (**3**) in quantitative yields. Unreacted ketene and ketene dimer were removed in vacuo. A precooled solution of 2.1–2.5 equiv of the aniline in acetone was then added slowly to the residue in a dropwise fashion. The mixture was stirred 1.5 h longer and stored at −78 °C overnight to complete the reaction. Recrystallization of the crude solid from methanol or ethanol afforded pure **4** in yields of 50–71%.

Sulfinamides **4** show typical infrared absorption (KBr) at 3050–3200 cm^{-1} (vs, amide NH), 1650–1670 cm^{-1} (vs, amide C=O), and 1050–1060 cm^{-1} (vs, S=O). Their ^1H NMR spectra in Me_2SO-d_6 exhibit a singlet at δ 4.08–4.16 attributable to the methylene protons and a multiplet at δ 7.15–7.45 indicative of the aromatic protons. In addition, the sulfinamide protons appear as sharp singlets at δ 9.02–9.07, and the amide protons appear as broad singlets at δ 10.2–10.65.

We next turned our attention to oxidation of the sulfi-

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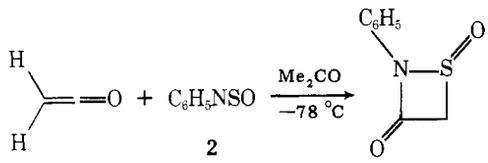

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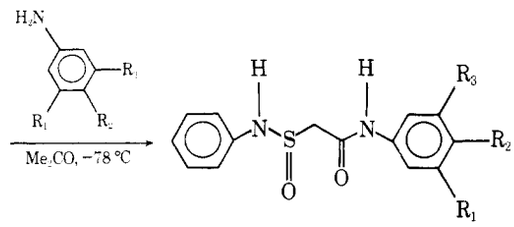
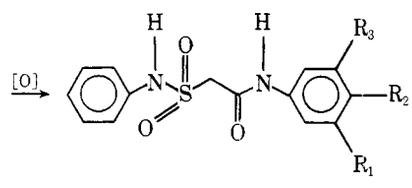


4

a, $R_1 = R_2 = R_3 = H$
b, $R_1 = R_3 = H$; $R_2 = CH_3$
c, $R_1 = CH_3$; $R_2 = R_3 = H$
d, $R_1 = R_3 = H$; $R_2 = F$



5

e, $R_1 = R_3 = H$; $R_2 = CF_3$
f, $R_1 = R_2 = R_3 = OCH_3$
g, $R_1 = R_2 = OCH_2O$; $R_3 = H$

namide moiety. Upon inspection of the literature, we were very much surprised to find that such oxidations had relatively little precedent. Oxidation of sulfinamides of the general structure RSONXY, where R = heterocyclic or aromatic nucleus with a *p*-amino group, X = acyl, hydrocarbon, or heterocyclic residue, and Y = hydrogen or a hydrocarbon residue, using potassium permanganate, hydrogen peroxide, or sodium peroxide was disclosed in a patent issued to Schering Corp. in 1949.[3] The only other sulfinamide oxidation was reported recently by Selling and Mak,[4] who converted 1-hexynylsulfinyl-*p*-toluidide to the corresponding sulfonamide in 72% yield with 2 mol equiv of *m*-chloroperbenzoic acid (MCPBA) in chloroform.

Our initial efforts centered on the oxidation of model compound **4c**, at 25–80 °C, with various mole ratios of MCPBA in methylene chloride. The highest yield (40%) of sulfonamide **5c** was obtained with 1.5 equiv of oxidant in the presence of powdered sodium bicarbonate. The low yield of product was attributed to decomposition of the sulfinamide under the acidic reaction conditions.[4-6] This was confirmed by the detection of aniline in the reaction mixture via thin-layer chromatography.

In an attempt to improve the yield of **5c**, other oxidizing agents were evaluated including aqueous potassium permanganate, aqueous sodium peroxide, ethanolic hydrogen peroxide, aqueous methanolic hydrogen peroxide with tungstic acid catalysis,[7] and aqueous methanolic sodium periodate. Unfortunately, all of the above systems afforded complex mixtures of products.

Finally, it was found that the oxidation could be successfully carried out in 73% yield at ambient temperature in methylene chloride with 6.6 mol equiv of 40% peracetic acid buffered with anhydrous sodium acetate. This method was used to convert the remaining sulfinamides into the corresponding sulfonamides **5** in yields ranging from 50 to 74%.

The infrared spectra of **5** in KBr are characterized by absorptions at 3250–3300 (m, sulfonamide NH), 3050–3060 (s, amide NH), 1670 (vs, amide C=O), 1308–1335 (vs, asym SO_2), and 1145–1155 cm^{-1} (vs, sym SO_2). The ^1H NMR spectra of **5** in acetone-d_6 are essentially the same as those of **4** save for the sulfonamide and amide proton resonances. The former appear as broad singlets at δ 8.58–8.72, while the latter appear as very broad singlets at δ 9.25–9.68.

With the exception of **5a**,[8] the reaction sequence described herein presently constitutes the only direct route to compounds of type **5**. Furthermore, the route utilizes readily available precursors and allows the introduction of diverse substituents. The members of series **4** and **5** are of potential pharmacological interest as novel antihypertensive or hypoglycemic agents.[9] Screening results for these compounds will be reported at a later time.

Experimental Section

All microanalyses were performed by Robertson Laboratories, Florham Park, N.J. Satisfactory analytical data (±0.3%, for C, H, N, and S) were obtained for all new compounds. Melting points were determined on a Thomas-Hoover Unimelt apparatus and are corrected. IR spectra were taken on a Perkin-Elmer Model 137 Infracord recording spectrophotometer. NMR spectra were determined on a Varian A-60A spectrometer. Chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane.

Materials. Ketene was generated by the pyrolysis of acetone over a nichrome coil at 500–700 °C in a calibrated ketene generator and collected at dry ice–acetone temperature. *N*-Sulfinylaniline was prepared from aniline and thionyl chloride according to the procedure of Michaelis and Hertz.[10] Peracetic acid was obtained from FMC Corp.

General Procedure. Synthesis of *N*-(3-methylphenyl)-2-[(phenylamino)sulfinyl]acetamide (**4c**). In a 250-mL, two-necked, round-bottomed flask equipped with a gas-inlet tube, dry-ice condenser, calcium chloride drying tube, and magnetic stirring bar were placed *N*-sulfinylaniline (4.18 g, 0.030 mol) and 150 mL of dry acetone. The solution was stirred and cooled to −78 °C, whereupon ketene was passed into the reaction flask at a rate of 0.20 mol/h for 15 min. The solution was stirred for 2 h at −78 °C, at which point unreacted ketene and ketene dimer were removed by slowly evacuating the system to 0.02 mm over a period of 1 h. A precooled solution of *m*-toluidine (7.50 g, 0.070 mol) in 50 mL of dry acetone was then added dropwise to the reaction vessel over a period of 45 min. The resulting mixture was stirred 1.5 h longer and then stored at −78 °C overnight to complete the reaction. After the reaction mixture was warmed to room temperature, the acetone was removed under reduced pressure and the crude product was refluxed for 40 min with 150 mL of ether. The resulting solid was collected and recrystallized from absolute alcohol to afford 5.83 g of **4c** as colorless needles: mp 154.3–155.3 °C. Concentration of the filtrate and recrystallization of the residue from absolute ethanol gave a second crop of product (0.31 g): mp 153.2–154.2 °C; total yield 6.14 g (71.0%).

Anal. Calcd for $C_{15}H_{16}N_2O_2S$: C, 62.48; H, 5.59; N, 9.71; S, 11.12. Found: C, 62.75; H, 5.77; N, 9.54; S, 10.94.

4a: 70.8% yield; mp 171.9–172.9 °C, lit.[2] mp 172–173 °C. **4b:** 61.4% yield; mp 175.7–176.7 °C, lit.[2] mp 181–182 °C. **4d:** 50.4% yield; mp 180.5–181.5 °C; Anal. Calcd for $C_{14}H_{13}FN_2O_2S$: C, 57.53; H, 4.45; N, 9.59; S, 10.96. Found: C, 57.69; H, 4.51; N, 9.69; S, 11.12. **4e:** 64.8% yield; mp 155.3–155.8 °C; Anal. Calcd for $C_{15}H_{13}F_3N_2O_2S$: C, 52.63; H, 3.83; N, 8.18; S, 9.36. Found: C, 52.65; H, 3.97; N, 8.43; S, 9.43. **4f:** 65.0% yield; mp 165.0–166.5 °C; Anal. Calcd for $C_{17}H_{20}N_2O_5S$: C, 56.04; H, 5.49; N, 7.69; S, 8.79. Found: C, 56.14; H, 5.61; N, 7.71; S, 8.81. **4g:** 66.5% yield; mp 161.2–162.2 °C; Anal. Calcd for $C_{15}H_{14}N_2O_4S$: C, 56.60; H, 4.43; N, 8.80; S, 10.07. Found: C, 56.88; H, 4.55; N, 9.01; S, 10.23.

General Oxidation Procedure. Synthesis of *N*-(3-methylphenyl)-2-[(phenylamino)sulfonyl]acetamide (**5c**). In a 50-mL three-necked round-bottomed flask equipped with a condenser, calcium chloride drying tube, thermometer, addition funnel, and magnetic stirring bar was dissolved 0.15 g of *N*-(3-methylphenyl)-2-[(phenylamino)sulfinyl]acetamide (0.52 mmol). The solution was cooled to 0 °C and mixed with 1.50 g of anhydrous sodium acetate (18.3 mmol). To the stirred suspension was then added a solution of peracetic acid (0.57 mL, 3.12 mmol, 40% in acetic acid) in 10 mL of methylene chloride over a period of 10 min. The mixture was stirred for 3 h at 0 °C and 21 h at ambient temperature, whereupon it was poured into a separatory funnel containing 35 mL of methylene chloride. The organic phase was separated and extracted successively

with 50 mL of 10% sodium sulfite solution, 3 × 50 mL of saturated sodium bicarbonate solution, and 100 mL of water. The organic phase was then dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure to afford 0.148 g of crude product. The product was purified by dissolving it in 3 mL of hot chloroform and subsequently precipitating it with 9 mL of petroleum ether: yield 0.116 g of near-colorless needles; mp 151.5–153.0 °C (73.2%).

Anal. Calcd for $C_{15}H_{16}N_2O_3S$: C, 59.19; H, 5.30; N, 9.20; S, 10.53. Found: C, 59.18; H, 5.38; N, 9.02; S, 10.58.

5a: 70.9% yield; mp 148.5–149.5 °C, lit.[8b] mp 150–151 °C. **5b:** 73.9% yield, mp 138.5–139.5 °C; Anal. Calcd for $C_{15}H_{16}N_2O_3S$: C, 59.19; H, 5.30; N, 9.20; S, 10.53. Found: C, 59.05; H, 5.39; N, 8.95; S, 10.75. **5d:** 63.9% yield; mp 182.3–183.8 °C; Anal. Calcd for $C_{14}H_{13}FN_2O_3S$: C, 54.54; H, 4.25; N, 9.08; S, 10.40. Found: C, 54.41; H, 4.32; N, 8.89; S, 10.56. **5e:** 64.5% yield; mp 223.5–225.5 °C; Anal. Calcd for $C_{15}H_{13}F_3N_2O_3S$: C, 50.28; H, 3.66; N, 7.82; S, 8.95. Found: C, 50.33; H, 3.71; N, 7.81. **5g:** 50.1% yield; mp 165.5–167.5 °C; Anal. Calcd for $C_{15}H_{14}N_2O_5S$: C, 53.89; H, 4.22; N, 8.38; S, 9.59. Found: C, 53.70; H, 4.25; N, 8.19; S, 9.61.

Registry No.—**1**, 463-51-4; **2**, 1122-83-4; **3**, 40328-82-3; **4a**, 23990-58-1; **4b**, 40328-83-4; **4c**, 66538-80-5; **4d**, 66538-81-6; **4e**, 66538-82-7; **4f**, 66538-83-8; **4g**, 66538-84-9; **5a**, 7117-27-3; **5b**, 66538-85-0; **5c**, 66538-86-1; **5d**, 66538-87-2; **5e**, 66538-88-3; **5f**, 66538-89-4; **5g**, 66538-69-0; *m*-toluidine, 108-44-1; aniline, 62-53-3; *p*-toluidine; 106-49-0; *p*-fluoroaniline, 371-40-4; *p*-trifluoromethylaniline, 455-14-1; 3,4,5-trimethoxyaniline, 24313-88-0; 5-amino-1,3-benzodioxole, 14268-66-7.

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Synthesis of Unsymmetrical Biphenyls via Aryl-Substituted 1,4-Cyclohexadienes

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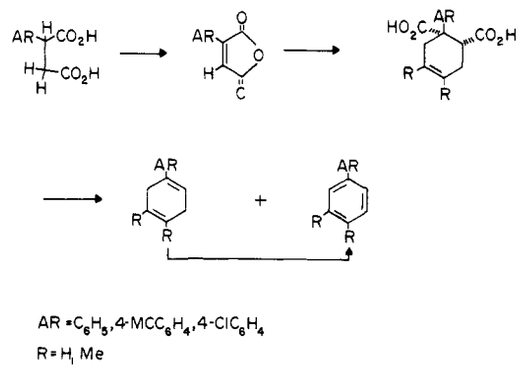
Because of a continuing interest in the chemistry and biological fate of biphenyl and especially unsymmetrically substituted biphenyls,[1] we had the need for a convenient synthesis of these compounds as well as the reduced 1-aryl-1,4-cyclohexadiene derivatives. The obvious use of the Birch reduction for the preparation of the dienes, in analogy with the successful reduction of simple substituted benzenes, has been discussed in the literature[2-4] and described to yield a difficultly separable mixture of dihydrophenyls and starting biphenyl. More recent investigation[5] of this process showed that the initially formed product of the Birch reduction of biphenyl is 1-phenyl-2,5-cyclohexadiene and that with appropriate care the compound could be isolated.

Since it appeared that this reductive type process was not efficient and would be even less so for more complex derivatives as well as suffering from the disadvantage of requiring as starting material the difficultly accessible unsymmetrical biphenyls, an alternative route was considered (Scheme I). This pathway involved the synthesis of a biphenyl nucleus incorporating functionality suitable for the regiospecific introduction of the unconjugated olefin. The bis dicarboxylic acid moiety may be considered a latent olefin function and transformation of this group to an olefin has been accomplished by the use of lead tetraacetate.[6] Although this process has been exploited most often in bicyclic systems, which preclude the possibility of further oxidation, it has been mentioned in passing that Δ^4-cyclohexene-1,2-dicarboxylic acid could be converted to 1,4-cyclohexadiene in 40% yield.[7]

Scheme I



Arylmaleic anhydrides, readily prepared from the appropriate substituted benzaldehydes via the succinic acid[8] followed in course by dehydrogenation[9] with selenium dioxide, condense readily with butadiene and 2,3-dimethylbutadiene. The products of this reaction have the substituted cyclohexene dicarboxylic acid function ready for conversion to the desired diene. Bis decarboxylation of these intermediates using lead tetracetate yeilded a mixture of diene and more completely oxidized biphenyl. Except for the parent, 1-phenyl-1,4-cyclohexadiene which yields a diene/biphenyl ratio of 5, the other derivatives all produce mixtures where the diene to biphenyl ratio is three or less. The identity of the diene component of these mixtures was determined by GC/MS which confirmed that the gross structure was indeed that of a biphenyl plus two hydrogens. In addition, the somewhat impure 1-phenylcyclohexadiene-1,4 had a melting point of 84–86 °C compared with the reported mp of 89 °C for this compound.[3]

The production of the fully aromatic biphenyl may arise by two different paths. The decarboxylation of the vicinal dicarboxylic group may occur either stepwise or in a concerted manner. The intermediate resulting from the loss of one carboxyl group may then lose a proton to yield a cyclodiene carboxylic acid which upon further decarboxylation would produce the biphenyl. A second possible route to the biphenyl is oxidation by lead tetracetate of the cyclodiene to the fully aromatic species, a process which has been shown to occur.[10]

Although this route is of only limited usefulness for the preparation of the aryl-substituted cyclodienes, it does suggest an entry into unsymmetrically substituted biphenyls. Oxidation of the diene/biphenyl mixture with DDQ occurs rapidly and cleanly, converting the mixture into homogeneous biphenyl. After simple chromatography of the reaction mixture analytically pure biphenyl is obtained.

Experimental Section

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. IR spectra were taken on a Model 621 Perkin-Elmer spectrometer. GLC analyses were done on a Varian series 2800 instrument equipped with a flame ionization detector and a 6 ft × ⅛ in. glass column packed with 3% OV 101 on 100/120 mesh Supelcoport. Mass spectra were obtained with a Fin-