(0.51 g, 2.0 mmol) under argon at −78 °C was added **33** (prepared from 0.290 mmol **25**) in dichloromethane (2.0 mL) dropwise over the course of 5 min. The cooling bath was removed after 10 min, and the mixture was allowed to warm to room temperature over 10.5 h. Water (10 mL) was added dropwise with rapid stirring to give a red mixture which was extracted with dichloromethane (2 × 10 mL). The combined organic phase was washed with water (2 × 10 mL) and brine (10 mL), dried, and evaporated to give **35** and **36** as a red-brown crystalline solid (33.9 mg, 41–56% from **25** depending on degree of debromination; NMR showed ~40% **36** based on integration of ring proton singlet). Characterization data of pure **36** and the controlled conversion of **35** to **36** is reported below.

(B) From 31. Quinone **20** (160 mg, 0.52 mmol) was reacted with pyrrolidine to give **31** as described earlier, and the product was immediately dissolved in dichloromethane (3 mL) under argon. After cooling the solution to −78 °C, boron tribromide (0.80 g, 3.1 mmol) was added dropwise over the course of 1 min with rapid stirring. The cold bath was removed 10 min later, and the reaction mixture was allowed to warm while being stirred in the dark over 15 h. Water (10 mL) was added dropwise with stirring, and the red mixture was partitioned between dichloromethane (8 mL) and 10% $NaHCO_3$ (8 mL). Acidification of the aqueous layer to pH 6 with 10% HCl followed by extraction with dichloromethane gave a combined organic solution which was washed with brine (10 mL) and dried. Evaporation gave **35** and **36** as a red-brown solid (111.0 mg, 75–103% from **20**, depending on the degree of debromination; NMR showed 50% **36** based on integration of ring proton singlet). This mixture was then hydrogenated (50 psi of H_2, Parr shaker, 65 mg of 5% Pd/C) in methanol (5 mL) for 15 h at which time the methanol was removed under a stream of nitrogen, and the residue was stirred under an air atmosphere with dichloromethane (8 mL) and 10% $NaHCO_3$ (8 mL) for 5 h. Filtration, separation of layers, and acidification of the aqueous phase to pH 6–7 gave a red mixture which was extracted with dichloromethane (3 × 5 mL). The combined organic solution was washed with brine (10 mL), dried, and evaporated to give red crystalline **36**: 46.9 mg (44% from dibromoquinone **20**); mp 200–201 °C (sublimed) (lit.[2] mp 196–197 °C); NMR δ 1.87 (s, 3 H, CH_3), 1.96 (m, 4 H, $NCH_2CH_2CH_2$), 3.6 (m, 4 H, CH_2NCH_2), 5.38 (s, 1 H, quinone H); IR (Nujol) 3215, 1650, 1610, 1447, 1420, 1397, 1387, 1339, 1325, 1307, 1248, 1206, 1068, 1046, 910, 816, 807, 799, 736, 727, 710 cm^{-1}; mass spectrum, found *m/e* 207.0890 (M^+), $C_{11}H_{13}NO_3$ requires *m/e* 207.0895.

2-Methyl-3-hydroxy-5-(1-pyrrolidinyl)-1,4-benzoquinone (37). To aminoquinone **11** (7.8 mg, 0.035 mmol) in dichloromethane (1.5 mL) at −78 °C under argon and with stirring was added boron tribromide (0.020 mL, 0.21 mmol). The cold bath was removed 10 min later, and the mixture was allowed to warm to room temperature. After 3.5 h the reaction was quenched by dropwise addition of water (10 mL). The mixture was extracted with dichloromethane (8 mL), and the aqueous phase was basified to pH 6 with 10% $NaHCO_3$. Extraction with dichloromethane (2 × 7 mL) was again performed, and the combined organic phase was washed with brine, dried, and evaporated to give **37** as a purple solid (4.6 mg, 64%) after chromatography: R_f (SiO_2, ether) 0.45; NMR δ 1.92 (s, 3 H, CH_3), 1.9 (m, 4 H, $NCH_2CH_2CH_2$), 3.6 (m, 4 H, CH_2NCH_2), 5.32 (s, 1 H, quinone H); IR (neat) 3165, 2941, 1667, 1597, 1577, 1567, 1451, 1379, 1330, 1318, 1300, 1229, 1185, 1155, 1139, 1104, 1044, 997, 821, 806, 754 cm^{-1}; mass spectrum, found *m/e* 207.0895 (M^+), $C_{11}H_{13}NO_3$ requires *m/e* 207.0895.

3-Methyl-4-methoxy-5-(1-pyrrolidinyl)-1,2-benzoquinone (38). Quinone **25** (172.1 mg, 0.555 mmol) was hydrogenated (50 psi of H_2, Parr shaker, 43 mg of 10% Pd/C) in methanol (10 mL) for 29 h after which time the solution was filtered and evaporated to give **30** as an amber oil (85 mg, 100%; R_f 0.15, dichloromethane/SiO_2), which decomposes in air. Anhydrous sodium sulfate (1.5 g), ether (8 mL), and pyrrolidine (55.6 μL, 0.666 mmol) were then added with rapid stirring. Argentous oxide (772 mg, 3.33 mmol) was added in one portion, and after 12 min the mixture was filtered. The salts were washed with ether, and the combined organic solution was evaporated to give **38** as red crystals: 99.3 mg (86%); R_f (SiO_2, CH_3CN) 0.21; NMR δ 1.8 (m, 4 H, $NCH_2CH_2CH_2$), 1.97 (s, 3 H, CH_3), 3.62 (m, 4 H, CH_2NCH_2), 3.77 (s, 3 H, OCH_3), 5.41 (s, 1 H, quinone H); IR (neat) 2979, 1672, 1610, 1529, 1456, 1418, 1381, 1330, 1312, 1305, 1218, 1176, 1006, 984, 891, 820, 754 cm^{-1}; mass spectrum, found *m/e* 221.1042, 223.1197 (M^+, M + 2), $C_{12}H_{15}NO_3$ requires *m/e* 221.1052, $C_{12}H_{17}NO_3$ (hydroquinone) requires *m/e* 223.1208.

2-Hydroxy-3-methyl-5-(1-pyrrolidinyl)-1,4-benzoquinone (36) from 38. Aminoquinone **38** (7.3 mg, 0.033 mmol) could be converted to **36** (3.3 mg, 48%) by the same procedure used to convert **11** to **37**.

Registry No. **4**, 6971-52-4; **5**, 2207-57-0; **6**, 19676-67-6; **7**, 25576-97-0; **9**, 77357-34-7; **10**, 77357-35-8; **11**, 77357-36-9; **12**, 77357-37-0; **13**, 77357-38-1; **14**, 77357-39-2; **15**, 77357-40-5; **16**, 77357-41-6; **17**, 77357-42-7; **18**, 77357-43-8; **20**, 77357-44-9; **21**, 77357-45-0; **22**, 1760-80-1; **23**, 77357-46-1; **24**, 77357-47-2; **25**, 77357-48-3; **26**, 77357-49-4; **27**, 77357-50-7; **30**, 77357-51-8; **31**, 77357-52-9; **32**, 77357-53-0; **33**, 77357-54-1; **35**, 77357-55-2; **36**, 4778-27-2; **37**, 77357-56-3; **38**, 77357-57-4; pyrrolidine, 123-75-1.

Synthesis and Stereochemistry of 3,5-Bis(carbomethoxy)-2,6-diphenyltetrahydro-4*H*-thiopyran-4-ones and Derivatives

Chin H. Chen,* George A. Reynolds, and Bernard C. Cossar

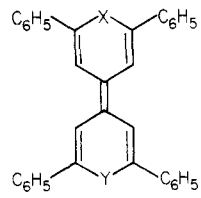
Research Laboratories, Eastman Kodak Company, Rochester, New York 14650

Received December 24, 1980

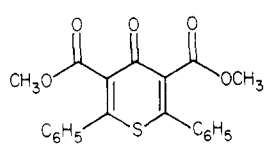
3,5-Bis(carbomethoxy)-2,6-diphenyl-4*H*-thiopyran-4-one (**2**) and its 5,6-*trans*-dihydro derivative **14** were synthesized by dehydrogenation with active manganese dioxide in refluxing chloroform of the corresponding diastereoisomeric mixture of *cis*- and *trans*-2,6-diphenyltetrahydro compounds **5** and **6**. The latter were prepared by the addition of hydrogen sulfide to dimethyl dibenzalacetonedicarboxylate (**4**). The stereochemistry and the reaction with *N*-chlorosuccinimide (NCS) of the diastereoisomers **5** and **6** and their corresponding sulfoxides **11** and **8** are elucidated. NCS reacted at the active methylene position in preference to the sulfide or sulfoxide function.

In connection with our interest in the synthesis of tetraphenyl-$\Delta^{4,4'}$-4*H*-heterobipyrans (**1**, X and Y = O and S),[1,2] we desired an efficient synthesis of the hitherto unknown 3,5-bis(carbomethoxy)-2,6-diphenyl-4*H*-thiopyran-4-one

0022-3263/81/1946-2752$01.25/0



1



2

(2) as a key intermediate in our synthetic schemes. This paper describes the successful synthesis of 2 and the stereochemistry and the attempted Pummerer reaction of the tetrahydro derivatives of 2[3] and their isomeric sulfoxides with *N*-chlorosuccinimide (NCS).

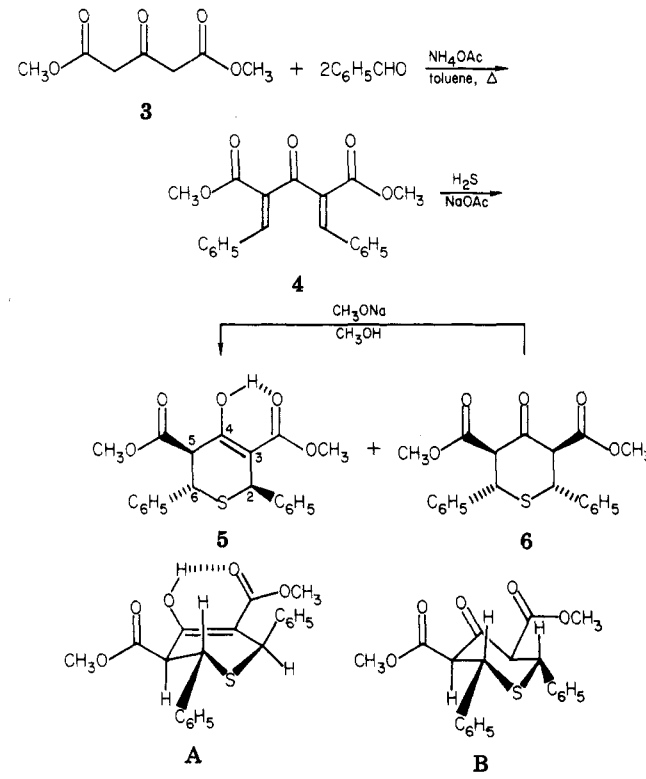
Results and Discussion

Synthesis and Stereochemistry of 3,5-Bis(carbomethoxy)-2,6-diphenyltetrahydro-4*H*-thiopyran-4-ones 5 and 6. In 1896, Knoevenagel[4] condensed dimethyl acetonedicarboxylate (3) with benzaldehyde with diethylamine as catalyst at room temperature to give quantitatively the bis(acetonedicarboxylate) adduct. With ammonium acetate in refluxing toluene, however, we obtained in 28% yield the desired dibenzylidene compound 4 by condensing 3 with 2 equiv of benzaldehyde (Scheme I). Treatment of 4 with H_2S in the presence of NaOAc in hot methanol produced in 72% yield the diastereoisomers 5 and 6 in a ratio of ca. 6:4 (GC assay); these products were readily separated by LC (silica gel, methylene chloride). The less polar isomer (R_f 0.5) was identified as the 2,6-*trans*-diphenylthiopyran 5, which exists totally in the enol form. This is supported by the IR (KBr) spectrum of 5, which has a broad enolic OH band at 3450 cm^{-1}, broad overlapping carbonyl bands for both carbomethoxy groups at 1740 cm^{-1}, and a broad C=C band at 1645 cm^{-1}. The deuterium-exchangeable enolic proton appears at δ 13.2 in the ^1H NMR of 5, which also has two nonequivalent methyl singlets at δ 3.61 and 3.64 and an AB quartet ($J_{5a,6a}$ = 11 Hz) at δ 4.01 and 4.27. The large coupling constant between the C-5 and C-6 hydrogens suggests that they are oriented trans diaxial to each other, and thus the large carbomethoxy and phenyl groups are assigned pseudo trans equatorial. A possible conformation that is consistent with the observed spectra of 5 is the half-chair A, similar to the one proposed for *trans*-2,6-diphenyl-5,6-dihydro-2*H*-thiopyran.[5]

The polar compound (R_f 0.18, silica gel, CH_2Cl_2), which has normal IR carbonyl bands for a ketone at 1715 cm^{-1} and an ester at 1745 cm^{-1}, is assigned the keto structure of *cis*-2,6-diphenylthiopyran 6. Its ^1H NMR spectrum is quite simple, owing to the presence of a plane of symmetry. The equivalent carbomethoxy groups resonate at δ 3.58, and the equivalent H_3, H_5 and H_2, H_6 appear as an AB quartet ($J_{2a,3a}$ = $J_{5a,6a}$ = 12 Hz) at δ 4.16 and 4.70, respectively. The large trans-diaxial coupling constant suggests that all the bulky substituents, carbomethoxy and phenyl, are equatorial, as expected in a chair conformation as in B.[6]

Examination of a stereomodel of the 6-enol form reveals that hydrogen bonding of the ester carbonyl with the hydroxy group would cause the C-3 methoxy group to interfere with the pseudoequatorial C-2 phenyl group. Therefore, 6 remains in the keto form against the normal tendency to enolize. On the other hand, since the C-2 phenyl group in 5 is pseudoaxial, which incurs no such interference, enolization occurs in 5.[7]

Scheme I

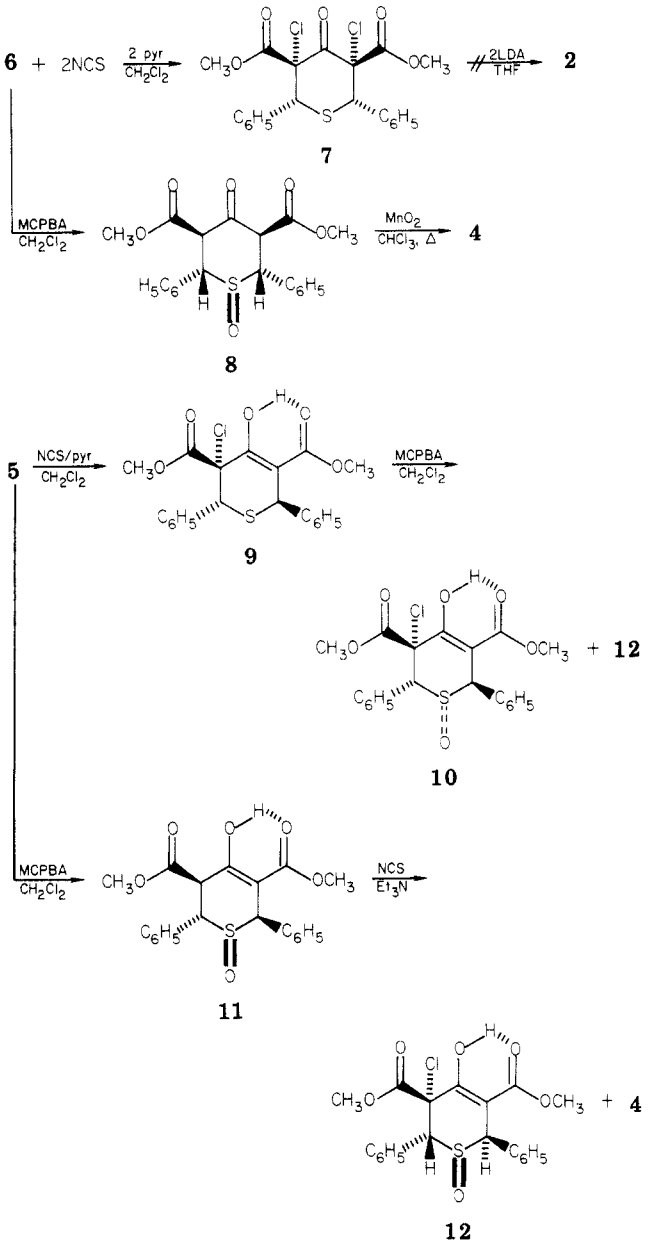


To determine which isomer is the thermodynamic product from the H_2S cyclization of 4, we treated the diastereoisomeric mixture of 5 and 6 (ca. 6:4) with sodium methoxide in methanol. ^1H NMR and TLC analyses of this reaction mixture after acid workup showed that most of 6 had isomerized to the enol 5, which was isolated in 72% yield. This result suggests that the *cis*-2,6-Ph_2-6 is a kinetically controlled product which, on further treatment with base, ring opens followed by reclosure to give the thermodynamic product, *trans*-2,6-Ph_2-5.

Stereochemistry of NCS Reactions of 5 and 6 and Their Corresponding Sulfoxides. Treatment of 6 with 2 equiv of NCS and pyridine[8] gave a chlorine-containing major product in 23% yield, to which we assigned the structure 7 on the basis of its elemental analysis ($C_{21}H_{18}O_5SCl_2$) and spectral data (Scheme II). The simplicity of its ^1H NMR spectrum, displaying the equivalent carbomethoxy groups at δ 3.77 (s) and the two equivalent benzylic protons as singlet at δ 5.2, immediately confirms the symmetry of this molecule. We note also a shift of 13 cm^{-1} to higher frequency of the ketone carbonyl absorption band of 7 at 1728 cm^{-1} (the corresponding $\nu_{C=O}$ for 6 is 1715 cm^{-1}). The relatively small shift is consistent with a structure in which both chlorine atoms occupy the axial positions[9] syn to the *cis*-2,6-diphenyl groups. This assignment is further supported by the ν_{C-Cl} band at 698 cm^{-1}, which is consistent with a structure bearing an axial

(1) Chen, C. H.; Reynolds, G. A. *J. Org. Chem.* **1980**, *45*, 2449, 2453, 2458.
(2) Perlstein, J. H. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 519.
(3) The oxygen analogue, 3,5-bis(carbomethoxy)-2,6-diphenyltetrahydro-4*H*-pyran-4-one, has been reported: Petrenko-Kritschenko, P.; Popiel, C. *J. Prakt. Chem.* **1899**, *60*, 157. However, no stereochemistry was studied.
(4) Knoevenagel, F. *Justus Liebigs Ann. Chem.* **1896**, *288*, 321.
(5) Henrichs, P. M.; Chen, C. H. *J. Org. Chem.* **1979**, *44*, 3591.
(6) Ramalingam, K.; Berlin, K. D.; Loghry, R. A.; VanderHelm, D.; Satyamurthy, N. *J. Org. Chem.* **1979**, *44*, 477.
(7) Mazza, D. D.; Reinecke, M. G. *J. Org. Chem.* **1981**, *46*, 128. We thank one of the reviewers for suggesting this rationale and providing us with this recent reference pertaining to a similar interaction.
(8) Chen, C. H.; Reynolds, G. A. *J. Org. Chem.* **1979**, *44*, 3144.
(9) Reisse, J.; Peters, P. A.; Ottinger, R.; Bervelt, J. P. *Tetrahedron Lett.* **1966**, 2511.

Scheme II

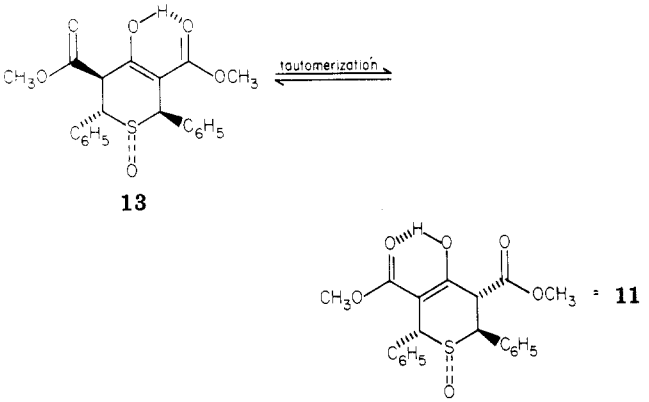


chlorine.[10] The spectral evidence also suggests that the substitution of two axial chlorines at C-3 and C-5 in **7** does not distort the symmetry and the preferred conformation of **6**. In addition, *these results show that the electrophile NCS reacts preferentially at the active methylene (enol) function rather than the sulfide.*[11]

m-Chloroperbenzoic acid (MCPBA) oxidized **6** in methylene chloride, giving the single sulfoxide **8** in 91% yield. Again, the spectral data are quite straightforward in support of the structure and the retention of symmetry in the molecule. The sulfoxide group is assigned equatorial, cis to the two equivalent axial H_2 and H_6 benzylic protons, on the basis of the evidence that a relatively small downfield shift[12] of the ^1H NMR of the α-benzylic protons is detected in changing solvents from deuteriochloroform to deuteriobenzene[13] ($\Delta\delta = \delta_{C_6D_6} - \delta_{CDCl_3} = 0.18$ ppm). The two axial H_3 and H_5 methine protons are remote from the deshielding effect of the sulfoxide group, and their chemical shift is not affected by the solvent change ($\delta_{C_6D_6} = \delta_{CDCl_3} = 4.53$ ppm). Furthermore, on steric grounds, the oxidation of **6** is expected to take place at the less hindered side[14] to give the equatorial sulfoxide **8**.

The *trans*-2,6-diphenyl enol reacted with NCS/pyr to give a monochloro-substituted product, to which we assigned the structure **9**, on the basis of elemental analysis ($C_{21}H_{18}ClO_5S$) and spectral evidence. The C–Cl band at 700 cm^{-1} in the IR (KBr) supports an axial-substituted chlorine which appears to impose little conformational change on **5**. The AB quartet due to the trans diaxial protons at H_5 and H_6 in the ^1H NMR spectrum of **5** was removed by the chlorine substitution, leaving one benzylic proton as a singlet at δ 4.49 for **9**. The other benzylic proton H_2, which was little affected by the chlorine substitution, remained as a singlet at $\delta \sim 5.0$. *m*-Chloroperbenzoic acid oxidation of **9** in methylene chloride produced a pair of ca. 1:1 diastereoisomeric sulfoxides **10** (R_f 0.53) and **12** (R_f 0.93), which were readily separated by preparative TLC (silica gel; EtOAc/CH_2Cl_2, 1:9 v/v). Both of these sulfoxides have the same elemental analyses ($C_{21}H_{19}ClO_6S$) and an IR C–Cl band at ca. 700 cm^{-1} for the axial-substituted chlorine.[10] Their ^1H NMR spectra are similar. The less polar sulfoxide is assigned the structure **12**, having the polar sulfinyl group oriented anti to the C-5 axial chlorine. The isomeric sulfoxide that is more polar is consistent with the structure **10**, having the sulfinyl function syn to the C-5 axial chlorine.

MCPBA oxidation of **5** produced only the single sulfoxide **11** in 89% yield. It is interesting to note that the isomeric sulfoxide **13**, which is a potential tautomeric form



of **11**, presumably formed first and is apparently not separable under the experimental conditions. However, we have no evidence to support the existence of **13**. Reaction of **11** with NCS in the presence of 1 equiv of triethylamine in methylene chloride at room temperature gave a mixture of products from which dimethyl 2,4-dibenzalacetonedicarboxylate (**4**, 43%) and a single monochloro sulfoxide (12%) were obtained. This sulfoxide is identical with the sulfoxide **12** isolated from the oxidation of **9**. The selective substitution of the chlorine at the active methylene position (C-5) of **11** is again demonstrated. The structure of **12** was confirmed by two observations: (1) the C-5 of the ^{13}C NMR spectrum of **11** at δ 46.31 (d) is shifted downfield to δ 73.0 (s) by substitution with chlorine in **12**; (2) a small

(10) Allinger, N. L.; Allinger, J.; Freiberg, L. A.; Czaja, R. F.; Lebel, N. A. *J. Am. Chem. Soc.* **1960**, *82*, 5876.

(11) Russell, G. A.; Mikol, G. J. In "Mechanism of Molecular Migrations"; Thyagarojan, B. S., Ed.; Interscience: New York, 1969; Vol. 2, pp 157–207.

(12) Lett, R.; Marquet, A. *Tetrahedron* **1974**, *30*, 3379. Geneste, P.; Olive, J. G.-L.; Ung, S. N. *Tetrahedron Lett.* **1975**, 2345. Fraser, R. R.; Durst, T.; McClory, M. R.; Viau, R.; Wigfield, Y. Y. *Int. J. Sulfur Chem., Part A* **1971**, *1*, 133.

(13) The sulfoxide **12** is not soluble in deuteriobenzene. The ^1H NMR spectrum was recorded in deuteriobenzene containing about 5% deuteriopyridine.

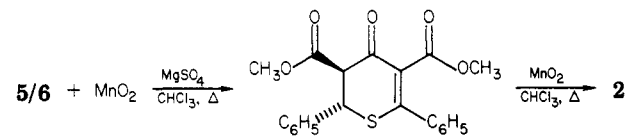
(14) Chen, C. H. *Tetrahedron Lett.* **1976**, 25. Carey, F. A.; Dailey, O. D., Jr.; Hernandez, O.; Tucker, J. R. *J. Org. Chem.* **1976**, *41*, 3975.

three-bond "CSCH" coupling is detected in the ^1H-coupled ^{13}C NMR spectrum of **12** involving the C-6 at δ 56.5 and the equatorial hydrogen H_2 as well as C-2 at δ 65.4 and the axial hydrogen H_6 (J = ~5.8 Hz).[15]

Treatment of the dichloroketo sulfide **7** with 2 equiv of lithium diisopropylamide (LDA) in THF at low temperature, however, failed to produce the desired **2**. Other bases such as pyridine and triethylamine were also unsuccessful in effecting the desired elimination. Attempted dehydrogenation of **8** with active MnO_2 in refluxing chloroform[16] or 1,2-dichloro-3,5-dicyanoquinone in refluxing tetrachloroethylene gave only the ring-opened product dimethyl dibenzalacetonedicarboxylate (**4**). The direct dehydrogenation of either the keto sulfide **6** or the enol sulfide **5** with selenium dioxide in refluxing toluene[17] was also not successful.

Under basic Pummerer conditions[11] with benzenesulfonyl chloride in pyridine at room temperature for 3 days, the keto sulfoxide **8** gave quantitatively the ring-opened dienone **4**. Trifluoroacetic anhydride readily reacted with either **8** or the enol sulfoxide **11** at room temperature to give a mixture of products. None of these products, however, corresponds to the desired 5,6-dihydro-4H-thiopyran-4-one **14**, which was successfully prepared later by another route. Also, the basic elimination of the monochloro-substituted enol sulfide **9** or the sulfoxide **12** was unfruitful. These negative results led us to explore other approaches toward the synthesis of **2**.

Synthesis of 3,5-Bis(carbomethoxy)-2,6-diphenyl-4H-thiopyran-4-one (2) and Its Dihydro Derivative 14. Active manganese dioxide in refluxing chloroform is an effective dehydrogenating agent for electron-deficient organic systems.[18] Indeed, heating the diastereoisomeric mixture of **5** and **6** with ~10 times by weight of active manganese dioxide[16] and anhydrous magnesium sulfate as a water scavenger in chloroform gave the 3,5-bis(carbomethoxy)-5,6-dihydro-2,6-diphenyl-4H-thiopyran-4-one (**14**) in 67% yield. The stereochemistry of the C-5 carbomethoxy group was assigned pseudoequatorial, trans to the C-6 phenyl group, on the basis of the ^1H NMR spectrum of **14**, in which the large coupling constant ($J_{5,6}$ = 12 Hz) between the H_5 at δ 4.13 and H_6 at δ 4.65 is consistent with a trans-diaxial configuration. Compound **14**, which exists totally in the keto form (IR $\nu_{C=O}$ 1608 cm^{-1}), can be further dehydrogenated with remarkable ease under the same reaction conditions with additional active manganese dioxide to give the desired 3,5-bis(carbomethoxy)-2,6-diphenyl-4H-thiopyran-4-one (**2**). For preparative purposes, however, **2** is best prepared directly from **5** and **6** by azeotropically refluxing a well-stirred chloroform suspension containing 18–20 times by weight of the active manganese dioxide. By this procedure, we routinely obtained **2** in ~50% yield directly from the diastereoisomeric mixture of **5** and **6** on a 3–4-g scale. Large-scale runs are not recommended, primarily because of the difficulty of handling the large amount of manganese dioxide and the reduced manganese, which tend to adsorb the product. If too little active manganese dioxide was used for this azeotropic procedure, a mixture of **2** and the dihydro derivative **14** was often obtained. They have identical R_f values (e.g., 0.34 on silica gel; EtOAc/hexane, 1:2 v/v) and solubilities and are almost impossible to separate. Therefore, TLC assay is ineffective in monitoring the reaction. ^1H NMR spectroscopy is an excellent means of following the dehydrogenation by the appearance of the two distinctive sharp singlets at δ 3.67 and 7.48 for the equivalent carbomethoxy groups and the aromatic protons, respectively. We also ran the same reaction starting from the pure isomer **5** or **6** and detected little difference in either reaction rates or yields.



14

Experimental Section

Melting points, obtained on a Mettler FPI instrument and a Thomas-Hoover melting point apparatus, are uncorrected. ^1H and ^{13}C NMR spectra of $CDCl_3$ solutions were recorded on a Varian EM-390 spectrometer and a Bruker WH-270 spectrometer, with Me_4Si as the internal standard. Mass spectra were obtained on an AEI MS-30 mass spectrometer. Field-desorption mass spectra were recorded on a Varian MAT-731 spectrometer. IR spectra were obtained on a Beckman IR 4250 spectrophotometer. Elemental analyses were done by the Analytical Sciences Division, Kodak Research Laboratories.

Dimethyl Dibenzalacetonedicarboxylate (4). A mixture of 17.4 g (0.1 mol) of dimethyl acetonedicarboxylate, 20.5 mL (0.2 mol) of benzaldehyde, 3 g of ammonium acetate, and 100 mL of toluene was refluxed, and the water that separated was collected. After 0.5 h of refluxing, the calculated amount of water was obtained. The reaction mixture was cooled, diluted with methylene chloride, and washed with water. The organic phase was separated and dried ($MgSO_4$), and the solvents were removed. The oily residue was stirred with petroleum ether, which caused it to become semisolid. This material was recrystallized twice from isopropyl alcohol, yielding 9.5 g (28%) of product: mp 133–134 °C; ^1H NMR ($CDCl_3$) δ 3.7 (s, 6 H, CH_3O), 7.36–7.5 (m, 12 H, Ar H and olefinic); IR (KBr) 1680 (α,β-unsaturated ketone C=O), 1720 (α,β-unsaturated ester C=O) cm^{-1}. Anal. Calcd for $C_{21}H_{18}O_5$: C, 72.0; H, 5.2. Found: C, 72.0; H, 5.0.

Diastereoisomers of 3,5-Bis(carbomethoxy)-2,6-diphenyltetrahydro-4H-thiopyran-4-ones (5 and 6). To a solution of 21 g (0.06 mol) of **4** in 300 mL of hot methanol was added 11 g of sodium acetate. A slow stream of hydrogen sulfide was passed through the refluxing solution for 6 h, and the mixture was allowed to stand overnight at room temperature. The white solid was collected; 16.5 g (72% yield).

The crude product was analyzed by gas chromatography on a 5% Dexsil column at 250 °C and showed 63% of **5** and 37% of the less volatile component **6**.

An 8-g sample of the crude material was purified by means of a Waters Prep LC 500 system, with methylene chloride as the eluent, and 3.2 g of **5** and 1.8 g of **6** were isolated.

3,5-Bis(carbomethoxy)-*cis*-2,*trans*-6-diphenyl-5,6-dihydro-4-hydroxy-2H-thiopyran (5). The first fraction of 3.2 g of **5** was recrystallized from methanol to give 3 g (38% based on the crude diastereoisomers) of pure **5** as white plates: mp 145–146 °C; IR (KBr) 3450 (br, OH), 1740 (br, ester C=O), 1645 (br, C=COH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.61 (s, 3 H, CH_3OCO), 3.64 (s, 3 H, CH_3OCO), 4.01 (d, 1 H, $J_{5,6\text{-diaxial}}$ = 11 Hz, H-5), 4.27 (d, 1 H, $J_{5,6\text{-diaxial}}$ = 11 Hz, H-6), 4.95 (s, 1 H, H-2 benzylic), 7.20–7.43 (m, 10 H, Ar H), 13.2 (s, 1 H, enol, deuterium exchangeable); ^{13}C NMR ($CDCl_3$) δ 41.96 (d, C-2), 42.17 (d, C-6), 52.20 (q, Me), 52.362 (q, Me), 55.77 (d, C-5), 101.84 (s, C-3), 127.12, 127.77, 128.32, 128.45, 128.89 (Ph), 138.53 (C-1′ Ph), 143.50 (C-1′ Ph), 170.28 (s, C-4), 170.98 (C=O), 171.68 (C=O); mass spectrum, m/e 384 (M^+). Anal. Calcd for $C_{21}H_{20}O_5S$: C, 65.6; H, 5.2; S, 8.3. Found: C, 65.4; H, 5.4; S, 8.3.

(15) A three-bond (^3J) coupling constant of 3–6.4 Hz has been reported for the "CCCH" system: Karabatsos, G. J.; Orzech, C. E., Jr. *J. Am. Chem. Soc.* **1965**, *87*, 560.

(16) Active MnO_2 was prepared according to a procedure described in: U.S. Patent 2459714, 1949. See also: Hyatt, J. A.; Krutak, J. J. *J. Org. Chem.* **1977**, *42*, 169.

(17) Chen, C. H. *Heterocycles* **1977**, *7*, 231. Chen, C. H.; Reynolds, G. A.; Van Allan, J. A. *J. Org. Chem.* **1977**, *42*, 2777.

(18) We thank Dr. J. A. Hyatt of the Tennessee Eastman Co. Research Laboratories for telling us his experimental results on the dehydrogenation of 4-(dicyanomethylene)cyclohexanone before publication.

3,*cis*-5-Bis(carbomethoxy)-*trans*-2,*trans*-6-diphenyltetrahydro-4*H*-thiopyran-4-one (6). The more polar fraction of 1.8 g of material was recrystallized from methanol, giving 1 g (13% yield based on the crude diastereoisomers) of pure **6** as white needles: mp 193–195 °C; IR (KBr) 1745 (br, ester C=O), 1715 (ketone C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.58 (s, 6 H, Me), 4.16 (d, 2 H, $J_{a,a}$ = 12 Hz, H-3 and H-5), 4.70 (d, 2 H, $J_{a,a}$ = 12 Hz, H-2 and H-6 benzylic), 7.26–7.37 (m, 10 H, Ar H); ^{13}C NMR ($CDCl_3$) δ 49.86 (d, C-2 plus C-6), 52.23 (q, Me), 65.28 (d, C-3 plus C-5), 127.83, 128.75, 129.11, 137.17 (Ph), 167.49 (ester C=O), 199.1 (keto C=O); mass spectrum, *m/e* 384 (M^+). Anal. Calcd for $C_{21}H_{20}O_5S$: C, 65.6; H, 5.2; S, 8.3. Found: C, 65.4; H, 5.6; S, 8.3.

Basic Isomerization of 6. A mixture of 1.92 g (5 mmol) of the mixed isomers **5** and **6** (ratio 63:37) and 10 mL of methanol was stirred under nitrogen for 20 h. The solution was acidified with concentrated hydrochloric acid, and the solid (1.41 g) was collected and recrystallized from methanol. The crude solid was nearly pure enol isomer **5** (by TLC), and recrystallization yielded 1.38 g (72%) of pure product (mp 145–146 °C) which was identical with an authentic sample. The mother liquors were evaporated, and TLC showed that the residue contained a very small amount of the keto isomer **6**.

3,*cis*-5-Dichloro-*trans*-3,*trans*-5-bis(carbomethoxy)-*cis*-2,*cis*-6-diphenyltetrahydro-4*H*-thiopyran-4-one (7). To a solution of 2 g (5.2 mol) of **6** and 0.82 g (2 equiv) of pyridine in 70 mL of methylene chloride was added 1.45 g (2 equiv) of *N*-chlorosuccinimide. The reaction mixture was stirred at room temperature for 22 h, washed with water, and dried ($MgSO_4$), and the solvent was evaporated to give a yellowish gummy solid. The solid was purified by column chromatography over alumina (Woelm, neutral activity III/20 mm, methylene chloride) to give 550 mg (23%) of pure **7**: mp 131 °C (hexanes); IR (KBr) 1765, 1746 (br, ester C=O), 1728 (ketone C=O), 698 (CCl) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.77 (s, 6 H, Me), 5.2 (s, 2 H, benzylic), 7.2–7.6 (m, 10 H, Ar H); ^{13}C NMR ($CDCl_3$) δ 51.26 (d, C-2 plus C-6), 53.83 (q, Me), 76.05 (s, C-3 plus C-5), 128.06 (d), 129.41 (d), 130.86 (d), 133.62 (s, Ph), 165.90 (s, carbomethoxy C=O), 189.96 (C-4 ketone C=O); mass spectrum, *m/e* 417 (M^+ – Cl), 385, 220. Anal. Calcd for $C_{21}H_{18}O_5SCl_2$: C, 55.6; H, 4.0; Cl, 15.7; S, 7.1. Found: C, 55.4; H, 4.1; Cl, 15.3; S, 7.0.

3,*cis*-5-Bis(carbomethoxy)-*trans*-2,*trans*-6-diphenyltetrahydro-4*H*-thiopyran-4-one *cis*-1-Oxide (8). To a solution of 100 mg (0.26 mmol) of the pure keto isomer **6** in 10 mL of methylene chloride was added dropwise a solution of 46 mg of *m*-chloroperbenzoic acid (MCPBA) in 2 mL of methylene chloride at room temperature. The reaction mixture was stirred for 30 min and washed with aqueous sodium bicarbonate, and the organic phase was evaporated. The residue was recrystallized from methanol, giving 95 mg (91%) of the sulfoxide **8**: mp 203–204 °C dec; ^1H NMR ($CDCl_3$) δ 3.58 (s, 6 H, Me), 4.52 (d, 2 H, $J_{a,a}$ = 14 Hz, H-3 and H-5), 4.85 (d, 2 H, J = 14 Hz, H-2 and H-6 benzylic), 7.38 (s, 10 H, Ar H); ^{13}C NMR ($CDCl_3$), δ 52.67 (Me), 53.97 (C-2 plus C-6), 64.04 (C-3 plus C-5), 128.40, 129.24, 129.44, 133.266 (Ph), 166.78 (C=O ester), 196.78 (C=O ketone); IR (KBr) 1746 (C=O ester), 1720 (C=O ketone), 1040 (S=O) cm^{-1}; ^1H NMR (C_6D_6 plus 5% pyr-d_5) δ 3.2 (s, 6 H, Me), 4.53 (d, 2 H, J = 14 Hz, H-3 and H-5), 5.03 (d, 2 H, J = 14 Hz, H-2 and H-6 benzylic), 7.18 (br s, 10 H, Ar H). Anal. Calcd for $C_{21}H_{20}O_6S$: C, 63.0; H, 5.0; S, 8.0. Found: C, 62.8; H, 5.1; S, 8.0.

5-Chloro-3,*trans*-5-bis(carbomethoxy)-*trans*-2,*cis*-6-diphenyl-5,6-dihydro-4-hydroxy-2*H*-thiopyran (9). To a solution of 500 mg (1.3 mmol) of **5** and 103 mg (1 equiv) of pyridine in methylene chloride was added 175 mg (1 equiv) of *N*-chlorosuccinimide. The reaction mixture was stirred at room temperature overnight, washed with water, and dried ($MgSO_4$), and the solvent was removed to give a yellowish gummy solid which was recrystallized from methanol (50 mL) to give 280 mg (52%) of pure **9**: mp 181.1 °C; mass spectrum, *m/e* 418 (M^+), 383 (M^+ – Cl); ^1H NMR ($CDCl_3$) δ 3.58 (s, 3 H, Me), 3.68 (s, 3 H, Me), 4.49 (s, 1 H, H-5), 5.05 (s, 1 H, H-2 benzylic), 7.21, 7.3 (2 br s, 10 H, Ar H), 13.05 (s, 1 H, deuterium-exchangeable enol); IR (KBr) 3440 (br, OH), 1764 (C=O ester), 1740 (C=O conjugated ester), 1660 (C=COH), 1225 (br, COC ester), 700 (CCl) cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 41.27 (d, C-2), 50.91 (d, C-5), 52.75 (q, Me), 53.47 (q, Me), 72.40 (s, C-6), 103.03 (s, C-3) 127.46, 127.69, 128.35, 128.55, 128.98 (Ph), 134.53 (s, C-1′ Ph), 140.26 (s, C-1′ Ph), 165.28 (s, enolic ester C=O), 169.55 (enolic C-4), 171.37 (s, ester C=O at C-5). Anal. Calcd for $C_{21}H_{19}ClO_5S$: C, 60.2; H, 4.5; S, 7.7. Found: C, 60.1; H, 4.5; S, 8.0.

5-Chloro-3,*trans*-5-bis(dicarbomethoxy)-*trans*-2,*cis*-6-diphenyl-5,6-dihydro-4-hydroxy-2*H*-thiopyran *trans*-1-Oxide (12). A solution of 2.9 g (7.25 mmol) of enol sulfoxide **11** and 810 mg (8 mmol) of triethylamine in 100 mL of methylene chloride was mixed with 1.02 g (7.65 mmol) of NCS at room temperature. The reaction mixture was stirred overnight, washed twice with water, and dried ($MgSO_4$), and the solvent was removed to give 3 g of brown oil. The oil was chromatographed (silica gel; EtOAc/hexane, 1:2 v/v) to give 1.1 g (43%) of dimethyl dibenzalacetonedicarboxylate (**4**), which was characterized by comparison with an authentic sample. Further elution with EtOAc/hexane (2:3 v/v) gave 550 mg of a yellow oil. This was rechromatographed by TLC (silica gel plate, 20 × 20 × 2 mm; EtOAc/hexane, 1:1 v/v) to give 160 mg (12%) of pure **12**: mp 194–195 °C dec (rate of heating ca. 10 °C/min; recrystallized from benzene/hexanes); IR (KBr) 3430 (br, OH), 1776 (C=O ester), 1732 (C=O ester), 1660 (C=COH), 1245 (br, COC ester), 1080 (S=O), 700 (CCl) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.65 (s, 3 H, Me), 3.77 (s, 3 H, Me), 4.17 (s, 1 H, H-3 methine), 5.54 (s, 1 H, H-6 benzylic), 7.25, 7.4 (2 br s, 10 H, Ar H), 13.22 (s, 1 H, deuterium-exchangeable enol); ^{13}C NMR ($CDCl_3$) δ 53.4 (q, Me), 54.1 (q, Me), 56.5 (dd, J_{CH} = 137 Hz, J_{CSCH} = 4 Hz), 65.4 (dd, J_{CH} = 140 Hz, J_{CSCH} = 5.8 Hz), 73.0 (s, CCl), 96.5 (s, C-3 olefinic), 128.6, 128.7, 128.9, 129.0, 129.3, 129.4, 130.4, 130.8 (Ph), 165.3 (s, C=O), 167.3 (s, =COH), 171.4 (s, C=O ester); field-desorption mass spectrum, *m/e* 434 (M^+ for $C_{21}H_{19}{}^{35}ClO_6S$). Anal. Calcd for $C_{21}H_{19}ClO_6S$: C, 58.0; H, 4.4; Cl, 8.2. Found: C, 58.5; H, 4.7; Cl, 8.5.

3,5-Bis(carbomethoxy)-*cis*-2,*trans*-6-diphenyl-5,6-dihydro-4-hydroxy-2*H*-thiopyran *cis*-1-Oxide (11). A solution of 0.768 g (2 mmol) of the enol sulfide **5** was oxidized by the method used for **6** with 1 equiv of *m*-chloroperbenzoic acid in methylene chloride to give 0.7 g (89%) of **11**: mp 167–168 °C dec; IR (KBr) 3440 (br, OH), 1732 (C=O ester), 1650 (br, C=COH), 1061 (br, S=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.6 (s, 3 H, Me), 3.68 (s, 3 H, Me), 4.08 (d, 1 H, $J_{5,6}$ = 12 Hz, H-5), 4.46 (d, 1 H, $J_{5,6}$ = 12 Hz, H-6), 5.36 (s, 1 H, H-2 benzylic), 7.1–7.6 (m, 10 H, Ar H), 13.2 (s, 1 H, deuterium-exchangeable enolic OH), which is consistent with the cis equatorial sulfoxide **11**; ^{13}C NMR ($CDCl_3$) δ 46.31 (d, C-5 and C-6; multiplicity determined by off-resonance coherent decoupling with decoupler set at 3 ppm upfield of Me_4Si), 52.48 (q, Me), 52.93 (q, Me), 62.15 (d, C-2), 92.03 (s, C-3), 128.47, 128.85, 129.01, 129.37, 130.60, 133.72 (Ph), 169.77 (C=O and C-4 enolic, overlapping), 172.363 (C=O). Anal. Calcd for $C_{21}H_{20}O_6S$: C, 63.0; H, 5.0; S, 8.0. Found: C, 63.1; H, 5.1; S, 7.9.

5-Chloro-3,*trans*-5-bis(carbomethoxy)-*trans*-2,*cis*-6-diphenyl-5,6-dihydro-4-hydroxy-2*H*-thiopyran *cis*-1-Oxide (10) and *trans*-1-Oxide (12). To a solution of 150 mg (0.36 mmol) of **9** in 20 mL of methylene chloride was added dropwise a solution of 73 mg of *m*-chloroperbenzoic acid in 2 mL of methylene chloride at room temperature. The reaction mixture was stirred for 1 h, washed with dilute $NaHCO_3$, dried ($MgSO_4$), and evaporated to give 164 mg of a diastereoisomeric mixture (ratio ca. 1:1 by ^1H NMR integration) of crude *trans*-sulfoxide **12** and *cis*-sulfoxide **10**. This mixture was separated by preparative TLC (silica gel; EtOAc/CH_2Cl_2, 1:9 v/v) to give pure **12**: ca. 30 mg; R_f 0.93; mp 194.5–195.5 °C dec (rate of heating ca. 10 °C/min); IR (KBr) and ^1H NMR ($CDCl_3$) spectra are superimposable with those of the authentic sample prepared from enol sulfoxide **11**.

The more polar spot (R_f 0.53) gave ca. 25 mg of *cis*-sulfoxide **10** (recrystallized from 3 mL of hexanes): mp 116 °C (sintered), 151.5–152.5 °C dec (rate of heating ~10 °C/min); ^1H NMR ($CDCl_3$) δ 3.64 (s, 3 H, Me), 3.72 (s, 3 H, Me), 3.99 (s, 1 H, H-6 benzylic), 5.47 (s, 1 H, C-2 benzylic), 7.2–7.5 (m, 10 H, Ar H), 13.36 (s, 1 H, deuterium-exchangeable enol); field-desorption mass spectrum, *m/e* 434 (M^+ for $C_{21}H_{19}{}^{35}ClO_6S$); IR (KBr) 3430 (br, OH), 1769 (C=O ester), 1748 (C=O conjugated ester), 1663 (C=COH), 1245 (br, COC ester), 1084 (S=O), 697 (CCl) cm^{-1}.

3,5-Bis(carbomethoxy)-5,6-dihydro-2,*trans*-6-diphenyl-4*H*-thiopyran-4-one (14). A mixture of 150 mg (0.39 mmol) of diastereoisomers **5** and **6**, 1.5 g of active manganese dioxide,[16] and 1.5 g of anhydrous magnesium sulfate in 50 mL of chloroform was refluxed for 7 h. The dark reaction mixture was filtered over anhydrous magnesium sulfate through a medium sintered-glass

funnel and washed with methylene chloride. The clear filtrate was evaporated to give a light yellowish solid, which was recrystallized from benzene/hexanes, giving 100 mg (67%) of pure **14**: mp 160–161 °C; IR (KBr) 1737 (C=O ester), 1728 (sh, C=O ester), 1608 (C=O dihydrothiopyrone) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.54 (s, 3 H, Me), 3.64 (s, 3 H, Me), 4.13 (d, 1 H, $J_{a,a}$ = 12 Hz, H-5 methine), 4.65 (d, 1 H, $J_{a,a}$ = 12 Hz, H-6 benzylic), 7.1–7.45 (m, 5 H, Ar H), 7.44 (br s, 5 H, Ar H). Anal. Calcd for $C_{21}H_{18}O_6S$: C, 66.0; H, 4.7; S, 8.4. Found: C, 65.6; H, 4.7; S, 8.5.

3,5-Bis(carbomethoxy)-2,6-diphenyl-4*H*-thiopyran-4-one (2). A mixture of 3.75 g (9.77 mmol) of diastereoisomers **5** and **6**, 67.5 g of active manganese dioxide,[16] and 400 mL of chloroform was azeotropically refluxed for 6 h (ca. 1.35 mL of water was collected). The reaction mixture was filtered over anhydrous magnesium sulfate, and the residue was washed with methylene chloride. The filtrate was evaporated to give 3.1 g of a solid, which was recrystallized from benzene/hexanes (1:2 v/v) to give 2 g (54%) of pure **2** as a white crystalline solid: mp 175–176 °C; IR (KBr) 1735 (C=O ester), 1729 (sh), 1605 (C=O thiopyrone) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.67 (s, 6 H, Me), 7.48 (s, 10 H, Ar H); mass spectrum, m/e 380 (M^+), 352 (M^+ – CO). Anal. Calcd for $C_{21}H_{16}O_5S$: C, 66.3; H, 4.2; S, 8.4. Found: C, 66.4; H, 4.4; S, 8.1.

The mother liquor was evaporated to give ca. 1 g of a yellow oil, from which one component was isolated by preparative TLC (CH_2Cl_2) and characterized as *trans*-methyl cinnamate:[19] mass spectrum, m/e 162 (M^+); ^1H NMR ($CDCl_3$) δ 3.8 (s, 3 H, Me), 6.4 (d, 1 H, J = 16 Hz), 7.65 (d, 1 H, J = 16 Hz), 7.15–7.6 (m, 5 H, Ar H).

Acknowledgment. We thank Frank M. Michaels of the Analytical Sciences Division of Kodak Research Laboratories for obtaining several key ^1H and ^{13}C NMR spectra on a Bruker WH-270 spectrometer.

Registry No. 2, 77461-74-6; **4**, 77461-75-7; **5**, 77461-76-8; **6**, 77461-77-9; **7**, 77461-78-0; **8**, 77461-79-1; **9**, 77461-80-4; **10**, 77461-81-5; **11**, 77461-82-6; **12**, 77519-43-8; **14**, 77461-83-7; *trans*-methyl cinnamate, 1754-62-7; dimethyl acetonedicarboxylate, 3298-40-6.

(19) The origin of *trans*-methyl cinnamate, which was formed only in small amounts from the active manganese dioxide oxidation of **5** and **6**, was not pursued further.

Absolute Configuration of 2,7-Diazaspiro[4.4]nonane. A Reassignment

C. G. Overberger* and David Wei Wang

Department of Chemistry and the Macromolecular Research Center, The University of Michigan, Ann Arbor, Michigan 48109

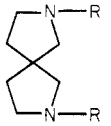
Richard K. Hill,* Grant R. Krow,[1] and David W. Ladner

Department of Chemistry, University of Georgia, Athens, Georgia 30602

Received January 14, 1981

The absolute configuration of the axially dissymmetric spirane 2,7-diazaspiro[4.4]nonane (**1**) has been elucidated as (*R*)-(–),(*S*)-(+) in chloroform by synthesis of both enantiomers from the centrodissymmetric intermediate **5**; the configuration of (*R*)-(–)-**5** was correlated with that of (*S*)-α-ethyl-α-methylsuccinic acid through the substituted pyrrolidine **11**. The configuration thus established for the sulfonamide derivative **2** is opposite to that derived earlier. The source of the original error is shown to lie in the preparation of spiroimide **14**, which is accompanied by almost total racemization when carried out at high temperatures. A more direct, efficient synthesis of **1** is described followed by resolution with dinitrodiphenic acid to give the optically pure enantiomers. Lowe's rule is shown to predict correctly the absolute configurations of several derivatives of **1** but not of **1** itself.

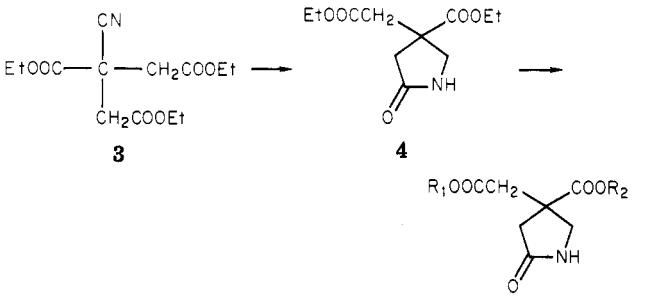
2,7-Diazaspiro[4.4]nonane (**1**), an axially dissymmetric molecule with C_2 symmetry, is similar to allenes and hindered biphenyls in possessing chirality without a formal chiral center. The determination of absolute configuration of molecules of this class has posed special problems because of the absence of an asymmetrically substituted carbon which might be related via chemical correlations to a standard of known configuration.[2] In 1968, in the first assignment of absolute configuration to a dissymmetric spiran, Krow and Hill[3] assigned the *S* configuration, according to the sequence rule of axial chirality, to the (–)-*N*,*N*-bis(*p*-toluenesulfonamide) (**2**) of **1** by synthesis



1, R = H
2, R = *p*-toluenesulfonyl

from a centrodissymmetric precursor. Reinvestigation of this synthesis has now shown that the assignment should be reversed. The details of the chemical correlation, the source of the initial misassignment, a new preparation of optically active **1**, and the corrected configurational assignment are presented in this paper.

Scheme I. Synthesis of Lactam 5



3 **4**

5, R_1 = H; R_2 = Et
6, R_1 = R_2 = H
7, R_1 = Et; R_2 = H
8, R_1 = CH_3; R_2 = Et

The key intermediate in the scheme to synthesize **1** from a centrodisymmetric precursor is lactam **5**; this is a chiral compound capable on the one hand of conversion to **1** without affecting the asymmetric center and, on the other hand, of chemical correlation with a configurational

(1) The portion of this work performed by Dr. Krow was carried out at Princeton University, Princeton, NJ.
(2) G. Krow, *Top. Stereochem.*, **5**, 31–68 (1970).
(3) G. Krow and R. K. Hill, *Chem. Commun.*, 430–431 (1968).

0022-3263/81/1946-2757$01.25/0