white crystals, mp 276.5–279 °C.

Anal. Calcd for $C_{16}H_{18}ClN$: C, 73.97; H, 6.98; N, 5.39. Found: C, 74.00; H, 7.06; N, 5.64.

The filtrate was concentrated and ether was added, producing 2.19 g more of white crystals (total 92%). NMR of the free amine (**11b**) ($CDCl_3$): δ 1.18 (d, 3 H), 1.45 (br, 1 H), 2.17–3.34 (m, 3 H), 3.85 (s, 2 H), 6.83–7.54 (m, 8 H).

2-Methyl-8-phenyl-1,2,3,4-tetrahydroisoquinoline (12a) Maleate. A mixture of 2.87 g (13.7 mmol) of 8-phenyl-1,2,3,4-tetrahydroisoquinoline (**11a**), 1.8 g of 90% formic acid, and 1.35 g of 37% aqueous formaldehyde was stirred at ambient temperature overnight and then warmed on a steam bath for 2 h. Concentrated hydrochloric acid (1.5 mL) was added, and the excess formic acid and formaldehyde were distilled off. The residue was taken up in water, and the solution was made alkaline with 50% sodium hydroxide and extracted with ether. The extract was washed with water and dried and the solvent was removed, yielding 3.00 g (98%) of clear colorless oil (**12a**): NMR ($CDCl_3$) δ 2.29 (s, 3 H), 2.62 and 2.96 ($A_2'B_2'$, m 4 H), 3.36 (s, 2 H), 6.85–7.48 (m, 8 H).

The oil was taken up in ether and treated with a saturated solution of maleic acid in ether. The crystals that separated were recrystallized from acetonitrile, yielding 4.35 g (93%) of white crystals of **12a** maleate, mp 146.5–147.5 °C.

Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.57; H, 6.31; N, 4.21.

2,3-Dimethyl-8-phenyl-1,2,3,4-tetrahydroisoquinoline (12b) Hydrobromide. A mixture of 3.10 g (13.9 mmol) of 3-methyl-8-phenyl-1,2,3,4-tetrahydroisoquinoline (**11b**), 1.8 g of 90% formic acid, and 1.4 g of 37% aqueous formaldehyde was reacted under the conditions described for **12a**, yielding 3.22 g of clear colorless oil of **12b**: NMR ($CDCl_3$) δ 1.12 (d, 3 H), 2.23 (s, 3 H), 2.71 (m, 3 H), 3.32 (d, 1 H, J = 16 Hz), 3.69 (d, 1 H, J = 16 Hz), 6.66–7.45 (m, 8 H).

The oil was taken up in ether and treated with saturated hydrogen bromide in ether to give 3.48 g of white powder that was recrystallized from ethanol/ether, yielding 3.19 g (72%) of **12b** hydrobromide, mp 190–192 °C.

Anal. Calcd for $C_{17}H_{20}BrN$: C, 64.15; H, 6.33; N, 4.40. Found: C, 63.74; H, 6.32; N, 4.38.

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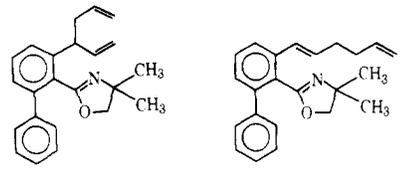
Registry No.—**2,** 69381-38-0; **3,** 57598-40-0; **3** HCl, 69381-39-1; **4,** 69381-40-4; **5a,** 69381-41-5; **5b,** 69381-42-6; **6a,** 69381-43-7; **6b,** 69381-44-8; **7a,** 69381-45-9; **7b,** 69381-46-0; **8a,** 69381-47-1; **8b,** 69381-48-2; **9a,** 69381-49-3; **9b,** 69381-50-6; **10a,** 69381-51-7; **10a** HCl, 69381-52-8; **10b,** 69381-53-9; **10b** HCl, 69381-54-0; **11a,** 69381-55-1; **11a** HCl, 69381-56-2; **11b,** 69381-57-3; **11b** HCl, 69381-58-4; **12a,** 69381-59-5; **12a** maleate, 69381-60-8; **12b,** 69381-61-9; **12b** HBr, 69381-62-0; biphenyl-2-carboxylic acid, 947-84-2; 2-amino-2-methylpropanol, 124-68-5; allyl bromide, 106-95-6; 3-ethyl-7-phenyl-1(3*H*)-isobenzofuranone, 69381-63-1; 2-(4,4-dimethyl-2-oxazolin-2-yl)-3-(1,5-hexadien-3-yl)biphenyl, 69381-64-2; ethylene oxide, 75-21-8; propylene oxide, 75-56-9.

References and Notes

(1) For examples, see (a) W. M. Whaley and T. R. Govendachari, *Org. React.*, **6,** Chapters 2 and 3 (1951); W. J. Gensler, *ibid.*, Chapter 4 (1951); (b) W. J. Gensler, *Heterocycl. Compd.*, **4,** Chapter 2 (1952).
(2) Y. Ahmad and D. H. Hey, *J. Chem. Soc.*, 3882 (1961).
(3) J. Sam, R. M. Shafik, and K. Aparajithan, *J. Pharm. Sci.*, **59,** 59 (1970).
(4) A. I. Meyers and E. D. Mihelich, *J. Org. Chem.*, **40,** 3158 (1975).
(5) H. W. Gschwend and A. Hamden, *J. Org. Chem.*, **40,** 2008 (1975).
(6) This biphenyloxazoline has been reported previously: A. I. Meyers and E. D. Mihelich, *J. Am. Chem. Soc.*, **97,** 7383 (1975). It was prepared by a different method, and no properties were given.
(7) This product (i) was further confirmed by Cope rearrangement to the linear 1,5-diene (ii). The NMR spectra were consistent for both structural assignments.



i ii

(8) (a) A. I. Meyers, Colorado State University, personal communication, 1978. (b) Similar methodology was recently reported [M. S. Newman, J. M. Khanna, K. Kanakarajan, and S. Kumar, *J. Org. Chem.*, **43,** 2553 (1978)] for the hydrolysis of a γ-hydroxyozazoline to a γ-lactone.
(9) For a review, see A. I. Meyers and E. D. Mihelich, *Angew. Chem., Int. Ed. Engl.*, **15,** 270 (1976).
(10) Melting points were taken in open capillaries on a Mel-Temp apparatus and are uncorrected. Spectra were recorded with a Beckman IR 12 infrared spectrometer and a Varian A-60d NMR spectrometer. Solvents were distilled off under reduced (aspirator) pressure, and anhydrous $MgSO_4$ was used as the drying agent. No attempts were made to maximize the yields of the reactions.
(11) NMR signals are indicated as s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet, and br = broad signal.

Convergent Approaches to Indoloquinones: Additions to Quinone Monoimides

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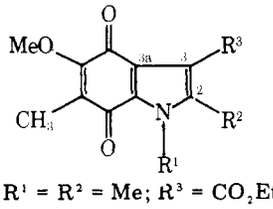
Indoloquinone **1a,** a model for more complex mitomycin analogues, was prepared by Michael addition of ethyl acetoacetate to quinone monoimide **12,** dehydration of the adduct **13** to indole **14,** and elaboration of the quinone functionality. The final oxidation step of **16b** to **1a** was accomplished with argentic oxide and aqueous nitric acid. Al alternative scheme failed in a model sequence when the amino benzofurans **6** could not be converted to indoles **7.**

A variety of synthetic endeavors have been directed toward mitomycins[1] and mitosenes,[2] as well as toward simple analogues[3] of these antibiotics. The challenge of developing a convergent synthesis of such functionalized indoloquinones (**1**) led us to consider an approach in which the key carbon–carbon bond (C-3,C-3a) is formed by the addition of an enol to a highly substituted benzoquinone derivative. Closure of the N,C-2 bond would complete the formation of the indole nucleus.[4]

Initial model work based on the addition of ethyl acetoac-



1a, $R^1 = R^2 = Me$; $R^3 = CO_2Et$

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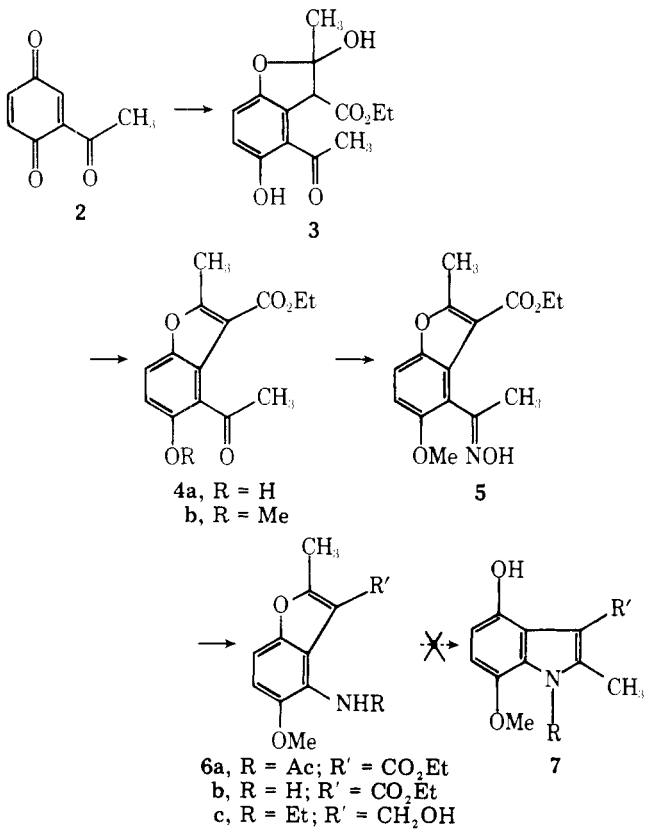
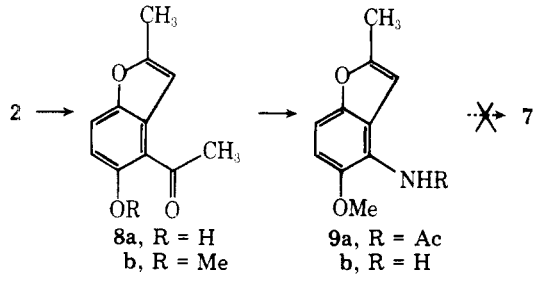
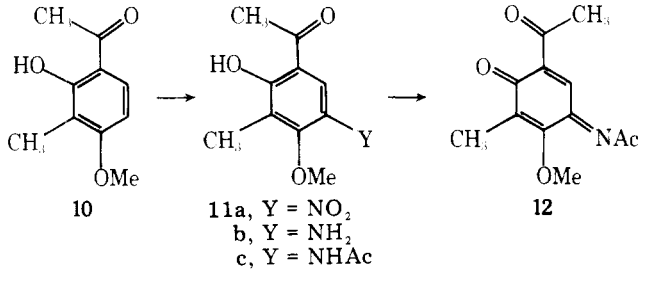
Scheme I



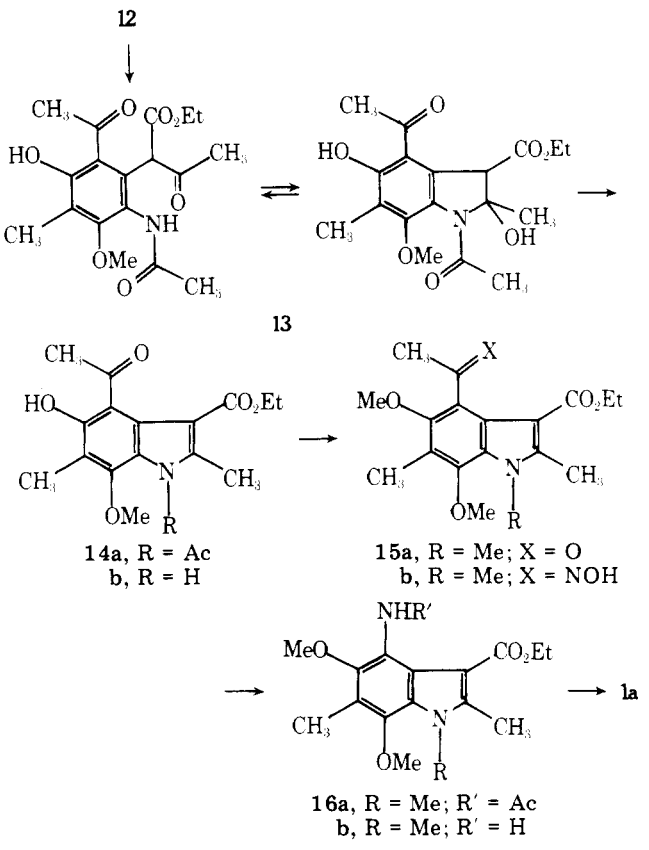
Scheme II



Scheme III



Scheme IV



etate to acetylbenzoquinone and elaboration of the adduct to the substituted benzofurans **6a–c** (Scheme I) was frustrated by our inability to convert any of these intermediates to an indole **7** (Scheme II).[5] Likewise, benzofurans **9** (see Experimental Section) were stable under a variety of conditions.

An alternative scheme in which ring closure of the adduct of a β-keto ester and a quinone monoimide affords an indole directly was employed to afford the desired indoloquinone (**1a**).[6a]

Quinone monoimide **12** was prepared according to Scheme III. The conversion of hydroxyacetanilide **11c** to quinone monoimide **12** was accomplished with $Pb(OAc)_4$.[6b]

Treatment of the quinone monoimide **12** with excess ethyl acetoacetate afforded a 1:1 adduct which appeared to be a mixture of isomers and, by analogy to products from similar reactions,[4] was assigned structure **13**. Acid-catalyzed dehydration gave the indole **14** in 73% yield from **12**.

The fully substituted ring system was then converted to the target compound **1a** by the sequence shown in Scheme IV. Rapid base hydrolysis of **14a** gave **14b**, which was methylated to afford **15a**. Oximation followed by Beckmann rearrangement afforded **16a**. Deacetylation gave the *p*-methoxyaniline **16b**, which was submitted to oxidation with argentic oxide and aqueous nitric acid.[7] Indoloquinone **1a** was isolated in 55% yield from **16b**.

To our knowledge, the transformation **16b** → **1a** is the first example of the synthesis of a quinone by the oxidative demethylation of a *p*-methoxyaniline.[8] The conversion of *p*-methoxyanilines to *p*-quinones by argentic oxide presumably proceeds by a mechanism analogous to the oxidative demethylation of hydroquinone methyl ethers (two pathways for this latter process have been suggested by Rapoport[7]) to give the quinone imine which hydrolyzes under the reaction conditions to **1a**.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and were uncorrected. Infrared spectra were recorded with a Perkin-Elmer Model 257 grating infrared spectrophotometer. Nuclear magnetic resonance measurements were carried out on a Varian A-60A instrument using tetramethylsilane as an internal reference. Ultraviolet absorption spectra were measured on a Cary 14 spectrophotometer. Mass spectra were determined on a Hitachi RMU-6D mass spectrometer.

Solvents and liquid reagents were routinely distilled before use. Reactions were performed in a dry nitrogen atmosphere.

Some samples were carried through several steps without recrys-

tallization. Analytical samples were prepared by recrystallization as indicated. Chromatography was performed using Merck silica gel (source: EM Laboratories). Preparative thin-layer chromatography (TLC) was performed using commercial plates spread with silica gel G (source: EM Laboratories).

4-Acetyl-3-carbethoxy-5-methoxy-2-methylbenzofuran (4b). To benzofuran **4a**[9] (2.00 g, 7.64 mmol) dissolved in 40 mL of dry acetone was added anhydrous potassium carbonate (2.60 g, 18.8 mmol) followed by 1.40 g (11 mmol) of dimethyl sulfate. The mixture was stirred at reflux for 2 h. The reaction mixture was filtered, 40 mL of MeOH was added, and the reaction mixture was stirred at room temperature overnight. Solvents were removed on a rotary evaporator, and the residue was partitioned between ether and saturated $NaHCO_3$ solution. The ether solution was washed with three portions of water and dried over $MgSO_4$. Concentration and recrystallization from hot hexane gave 1.95 g (92%) of a white solid: mp 89–90 °C; IR ($CHCl_3$) 1697, 1590 cm^{-1}; NMR ($CDCl_3$) δ 1.32 (t, J = 7 Hz, 3 H), 2.58 (s, 3 H), 2.72 (s, 3 H), 3.83 (s, 3 H), 4.30 (q, J = 7 Hz, 2 H), 6.88 (d, J = 9 Hz, 1 H), 7.35 (d, J = 9 Hz, 1 H). Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.20; H, 5.84. Found: C, 65.06; H, 5.99.

4-Acetyl-3-carbethoxy-5-methoxy-2-methylbenzofuran Oxime (5). To a stirred solution of **4b** (1.70 g, 6.16 mmol) dissolved in 20 mL of absolute ethanol and 20 mL of pyridine was added hydroxylamine hydrochloride (1.70 g, 25 mmol). The reaction mixture was stirred at reflux for 5 h. Ethanol and pyridine were evaporated, and the residue was dissolved in ether. The organic solution was washed with saturated $NaHCO_3$ solution and three portions of water and dried over $MgSO_4$. The reaction mixture was concentrated. Recrystallization from hexane gave 1.61 g (90%) of a yellow solid: mp 115–116 °C; IR ($CHCl_3$) 3258, 1693, 1589 cm^{-1}; NMR ($CDCl_3$) δ 1.32 (t, J = 7 Hz, 3 H), 2.22 (s, 3 H), 2.68 (s, 3 H), 3.82 (s, 3 H), 4.28 (q, J = 7 Hz, 2 H), 6.91 (d, J = 9 Hz, 1 H), 7.32 (d, J = 9 Hz, 1 H), 7.94 (br s, NOH).

4-Acetamino-3-carbethoxy-5-methoxy-2-methylbenzofuran (6a). To a stirred solution of benzofuran **5** (1.30 g, 4.46 mmol) in 25 mL of dry benzene at room temperature was added 1.43 g (6.88 mmol) of phosphorus pentachloride at room temperature (addition required 5 min). The reaction mixture was quenched with H_2O and concentrated. Recrystallization from hot H_2O gave 1.15 g (88%) of a white solid: mp 143–145 °C; IR ($CHCl_3$) 3300, 1682 cm^{-1}; NMR ($CDCl_3$) δ 1.43 (t, J = 7 Hz, 3 H), 2.17 (s, 3 H), 2.67 (s, 3 H), 3.83 (s, 3 H), 4.38 (q, J = 7 Hz, 2 H), 6.95 (d, J = 9 Hz, 1 H), 7.23 (d, J = 9 Hz, 1 H). Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.80; H, 5.93; N, 4.76.

4-Amino-3-carbethoxy-5-methoxy-2-methylbenzofuran (6b). Concentrated HCl (0.10 mL) was added dropwise to a stirred solution of **6a** (76 mg, 0.26 mmol) in 5 mL of EtOH. The resulting solution was stirred at reflux for 24 h. EtOH was evaporated, and the residue was partitioned between saturated $NaHCO_3$ solution and ether. The organic phase was washed with saturated NaCl solution and H_2O and dried over anhydrous $MgSO_4$. Removal of ether gave 73 mg of the crude product, which was purified by preparative TLC using benzene–ether (1:1) to give 61 mg (95%) of a white solid, mp 81–82 °C. An analytical sample, mp 82–83 °C, was obtained by recrystallization from hot EtOH: IR ($CHCl_3$) 3463, 3344, 1679, 1612, 1573 cm^{-1}; NMR ($CDCl_3$) δ 1.34 (t, J = 7 Hz, 3 H), 2.68 (s, 3 H), 3.88 (s, 3 H), 4.32 (q, J = 7 Hz, 2 H), 5.64 (br s, 2 H), 6.64 (d, J = 9 Hz, 1 H), 6.83 (d, J = 9 Hz, 1 H). Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.50; H, 6.20; N, 5.57.

4-(Ethylamino)-3-(hydroxymethyl)-5-methoxy-2-methylbenzofuran (6c). In a 25-mL dry flask fitted with an addition funnel, reflux condenser, and magnetic stirrer was placed 60 mg (1.6 mmol) of lithium aluminum hydride. To this was added 172 mg (0.59 mmol) of benzofuran **6a** in 10 mL of dry ether. The mixture was stirred at room temperature for 3 h, cooled to 0 °C, and quenched with wet ether. Filtration gave an ether solution which was washed with saturated NaCl solution and H_2O and dried over anhydrous $MgSO_4$. Solvent was removed and the residue was submitted to chromatography. Elution with benzene–ether (1:1) gave 125 mg of a yellow oil (90%). Crystallization from petroleum ether at low temperature gave a white solid: mp 58–59 °C; IR ($CHCl_3$) 3410 cm^{-1} (broad); NMR ($CDCl_3$) δ 1.29 (s, J = 7 Hz, 3 H), 2.37 (s, 3 H), 3.13 (q, J = 7 Hz, 2 H), 3.84 (s, 3 H), 4.68 (s, 2 H), 5.16 (s, 2 H), 6.88 (d, J = 9 Hz, 1 H), 7.18 (d, J = 9 Hz, 1 H). Anal. Calcd for $C_{13}H_{17}NO_5$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.28; H, 7.46; N, 5.84.

4-Acetyl-5-hydroxy-2-methylbenzofuran (8a). A solution of acetylbenzoquinone (447 mg, 2.98 mmol) dissolved in neat isopropenyl methyl ether (4 mL) was stirred at room temperature under N_2 for an hour. The reaction mixture was concentrated and filtered through silica gel. The crude product was stirred for 3 h with 500 mg of *p*-toluenesulfonic acid in 10 mL of refluxing benzene under a Dean-Stark trap. The reaction mixture was cooled, washed with saturated $NaHCO_3$ solution and H_2O, and dried over anhydrous $MgSO_4$. Concentration and chromatography using benzene–ether (8:1) gave 473 mg of a yellow solid (84% from **2**), mp 104–105 °C. An analytical sample was obtained by recrystallization from ether and then from a mixture of petroleum ether and THF: IR ($CHCl_3$) 1600 cm^{-1}; NMR ($CDCl_3$) δ 2.46 (s, 3 H), 2.64 (s, 3 H), 6.54 (s, 1 H), 6.81 (d, J = 9 Hz, 1 H), 7.52 (d, J = 9 Hz, 1 H), 12.0 (s, 1 H). Anal. Calcd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.77; H, 5.51.

4-Acetyl-5-methoxy-2-methylbenzofuran (8b). To a solution of **8a** (128 mg, 0.67 mmol) in 5 mL of dry acetone was added anhydrous potassium carbonate (185 mg, 1.34 mmol) and 100 mg (0.79 mmol) of dimethyl sulfate. The reaction mixture was stirred at reflux overnight, cooled, and filtered. Methanol (5 mL) was added, and the reaction mixture was stirred overnight at room temperature. Solvents were removed, and the residue was partitioned between ether and H_2O. The organic phase was dried over $MgSO_4$ and concentrated. Crystallization from petroleum ether gave 121 mg (88%) of **8b:** mp 54–55 °C; IR ($CHCl_3$) 1656 cm^{-1}; NMR ($CDCl_3$) δ 2.42 (s, 3 H), 2.63 (s, 3 H), 3.87 (s, 3 H), 6.86 (d, J = 9 Hz, 1 H), 6.97 (br s, 1 H), 7.48 (d, J = 9 Hz, 1 H). Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.58; H, 5.92. Found: C, 70.20; H, 6.08.

4-Acetamino-5-methoxy-2-methylbenzofuran (9a). To a stirred solution of **8b** (251 mg, 1.25 mmol) in 3 mL of EtOH and 3 mL of pyridine was added hydroxylamine hydrochloride (200 mg, 2.88 mmol). The reaction mixture was stirred at reflux for 3 h. EtOH and pyridine were removed under reduced pressure, and the residue was dissolved in ether. This solution was washed three times with water and dried over $MgSO_4$. A quantitative yield (274 mg) of crude oxime (mp 193–195 °C, IR (KBr) 3150 cm^{-1}) was obtained.

To a solution of the crude oxime in 15 mL of dry benzene was added 350 mg (1.68 mmol) of phosphorus pentachloride. After being stirred for 15 min at room temperature, the reaction mixture was quenched with H_2O and saturated $NaHCO_3$ solution. Partitioning between benzene and NaCl solution gave an organic solution which was washed with H_2O and dried over anhydrous $MgSO_4$. After concentration the residue was subjected to chromatography. Elution with benzene–ether (1:1) gave 163 mg (61% overall) of benzofuran **9a** as a white solid, mp 162–163 °C. An analytical sample was obtained by crystallization from EtOH–H_2O: IR ($CHCl_3$) 3418, 1670 cm^{-1}; NMR ($CDCl_3$) δ 2.14 (s, 3 H), 2.37 (s, 3 H), 3.80 (s, 3 H), 6.48 (s, 1 H), 6.77 (d, J = 9 Hz, 1 H), 7.18 (d, J = 9 Hz, 1 H). Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C 65.54; H, 6.12; N, 6.28.

4-Amino-5-methoxy-2-methylbenzofuran (9b). A solution of **9a** (138 mg, 0.63 mmol) in 1 mL of ethanol and 4.0 mL of 30% NaOH was stirred at reflux for 5 h. Ethanol was evaporated, and the residue was partitioned between ether and H_2O three times. The organic phase was dried over anhydrous $MgSO_4$. The crude product was subjected to chromatography. Elution with benzene–ether (1:1) gave 104 mg (94%) of a white solid: mp 84–85 °C; IR ($CHCl_3$) 3450, 3375 cm^{-1}; NMR ($CDCl_3$) δ 2.33 (s, 3 H), 3.78 (s, 3 H), 3.90 (s, 2 H), 6.12 (s, 1 H), 6.75 (d, J = 9 Hz, 1 H), 7.24 (d, J = 9 Hz, 1 H). Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.66; H, 6.41; N, 7.70.

2-Hydroxy-5-nitro-4-methoxy-3-methylacetophenone (11a). To a solution of **10**[10] (2.25 g, 12.5 mmol) in 12.0 mL of glacial acetic acid at 0 °C was added 5.2 mL of concentrated HNO_3 (70%). The solution was stirred at 10–20 °C for 3 h and then was poured into ether. The resulting solution was washed with H_2O four times, dried over $MgSO_4$, and concentrated. Crystallization from EtOH gave 1.14–1.54 g (40–55% yield) of **11a:** mp 110 °C; IR ($CHCl_3$) 3430, 1533, 1325 cm^{-1}; NMR ($CDCl_3$) δ 2.24 (s, 3 H), 2.70 (s, 3 H), 3.95 (s, 3 H), 8.39 (s, 1 H), 13.1 (s, 1 H). Anal. Calcd for $C_{10}H_{11}NO_5$: C, 53.33; H, 4.92; N, 6.22. Found: C, 53.30; H, 5.13; N, 6.18.

5-Amino-2-hydroxy-4-methoxy-3-methylacetophenone (11b). A solution of **11a** (323 mg, 1.43 mmol) in 25 mL of absolute EtOH was treated with hydrogen (10% Pd–C, 140 mg) at atmospheric pressure. The reaction mixture was filtered, 0.5 mL of 10% HCl solution was added, and EtOH was evaporated. The residue was partitioned between saturated sodium bicarbonate and ether, and the organic phase was washed with H_2O and dried over $MgSO_4$. Removal of ether gave 248 mg of a white solid (89%): mp 80–81 °C; IR ($CDCl_3$) 3360, 3418, 1590 cm^{-1}; NMR ($CDCl_3$) δ 2.18 (s, 3 H), 2.50 (s, 3 H), 3.59 (s, 2 H), 3.78 (s, 3 H), 6.92 (s, 1 H), 12.4 (s, 1 H).

5-Acetamino-2-hydroxy-4-methoxy-3-methylacetophenone (11c). To a solution of **11b** (7.00 g, 35.9 mmol) in 100 mL of dry pyridine at 0 °C was slowly added 3.6 mL (40.0 mmol) of acetic anhydride. The reaction mixture was stirred at 0 °C for 0.5 h, and then pyridine and acetic anhydride were removed by concentration and ether was

added. The resulting solution was washed with H_2O, dried over $MgSO_4$, and concentrated. The residue was subjected to chromatography. Elution with benzene–ether (1:1) gave 7.87 g (93%) of a white solid: mp 140–141 °C (from EtOH); IR ($CHCl_3$) 3425, 1661, 1615 cm^{-1}; NMR ($CDCl_3$) δ 2.18 (s, 3 H), 2.24 (s, 3 H), 2.58 (s, 3 H), 3.81 (s, 3 H), 7.78 (s, 1 H), 8.55 (s, 1 H), 12.6 (s, 1 H). Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.62; H, 6.39; N, 5.78.

5-Acetyl-2-methoxy-3-methyl-*p*-quinone Monoacetimide (12). A suspension of **11c** (107 mg, 0.45 mmol) and 190 mg (0.45 mmol) of dry lead tetracetate in 10 mL of dry chloroform was stirred at reflux for 80 min. The reaction mixture was filtered, and the filtrate was concentrated. The residue was subjected to chromatography. Elution with benzene–ether (1:1) gave 97 mg (91%) of a yellow oil: IR ($CHCl_3$) 1682, 1662, 1635, 1612 cm^{-1}; NMR ($CDCl_3$) δ 2.02 (s, 3 H), 2.24 (s, 3 H), 2.54 (s, 3 H), 3.87 (s, 3 H), 7.22 (s, 1 H).

Ethyl 1,4-Diacetyl-5-hydroxy-7-methoxy-2,6-dimethyl-3-indolecarboxylate (14a). To a solution of **12** (97 mg, 0.41 mmol) in 3 mL of dry benzene was added 0.27 mL (5 equiv) of ethyl acetoacetate. The reaction mixture was stirred for 2 days at room temperature and then was concentrated and subjected to chromatography. Elution with benzene–ether (1:1) followed by ethyl acetate gave 135 mg of material which showed two overlapping spots on TLC: IR ($CHCl_3$) 3430, 1712, 1685, 1624 cm^{-1}; NMR ($CDCl_3$) δ 1.20 (t, J = 7 Hz), 1.71 (s), 1.83 (s), 2.02 (s), 2.06 (s), 2.20 (s), 2.37 (s), 3.76 (s), 4.14 (complex m), 7.21 (br s, exchanges in D_2O), 12.70 (s, exchanges in D_2O), 13.11 (s, exchanges in D_2O). This material was dissolved in 7.0 mL of absolute EtOH; 0.2 mL of concentrated HCl was added, and the solution was stirred at reflux for 25 min. Then it was cooled to room temperature and concentrated. The residue was partitioned between ether and sodium bicarbonate solution. The organic phase was concentrated. Chromatography with benzene–ether (1:1) as eluent gave 105 mg (73%) of a yellow oil which crystallized from petroleum ether at −78 °C: mp 66–67 °C; IR ($CHCl_3$) 1748, 1709, 1692 cm^{-1}; NMR ($CDCl_3$) δ 1.33 (t, J = 7 Hz, 3 H), 2.25 (s, 3 H), 2.37 (s, 3 H), 2.56 (s, 3 H), 2.66 (s, 3 H), 3.74 (s, 3 H), 4.32 (q, J = 7 Hz, 2 H), 11.3 (s, 1 H). Anal. Calcd for $C_{18}H_{21}NO_6$: C, 62.23; H, 6.09; N, 4.03. Found: C, 62.06; H, 6.31; N, 3.96.

Ethyl 4-Acetyl-5-hydroxy-7-methoxy-2,6-dimethyl-3-indolecarboxylate (14b). To a solution of **13a** (220 mg, 0.63 mmol) in 1.5 mL of EtOH was added 6.5 mL of 30% NaOH solution. The resulting solution was stirred at reflux for 10–15 min. Concentration gave a residue which was partitioned between ether and sodium bicarbonate solution. The organic phase was washed with H_2O, dried over $MgSO_4$, and concentrated. Chromatography using benzene–ether (1:1) as eluent gave 173.0 mg (90%) of a yellow solid: mp 155–156 °C (from ether and petroleum ether); IR ($CHCl_3$) 3447, 3272, 1692, 1627 cm^{-1}; NMR ($CDCl_3$) δ 1.32 (t, J = 7 Hz, 3 H), 2.12 (s, 3 H), 2.43 (s, 3 H), 2.68 (s, 3 H), 3.90 (s, 3 H), 4.33 (q, J = 7 Hz, 2 H), 9.77 (br s, 1 H), 11.61 (br s, 1 H); mass spectrum, m/e (M^+) 305. Anal. Calcd for $C_{16}H_{19}NO_5$: C, 62.96; H, 6.27; N, 4.58. Found: C, 62.79; H, 6.36; N, 4.73.

Ethyl 4-Acetyl-5,7-dimethoxy-1,2,6-trimethyl-3-indolecarboxylate (15a). To a solution of **13b** (603 mg, 1.97 mmol) in 30 mL of dry acetone was added 1.50 g (11 mmol) of anhydrous potassium carbonate followed by 1.00 g (7.9 mmol) of dimethyl sulfate. The reaction mixture was stirred at reflux overnight, cooled, and filtered. Excess (30 mL) MeOH was added, and the solution was stirred at room temperature overnight. Concentration gave a residue which was partitioned between ether and H_2O. The organic phase was dried over $MgSO_4$ and concentrated. Chromatography with benzene–ether (1:1) gave 614 mg (93%) of a yellow solid: mp 111–112 °C (from hexane and CH_2Cl_2); IR ($CHCl_3$) 1698, 1687 cm^{-1}; NMR ($CDCl_3$) δ 1.36 (t, J = 7 Hz, 3 H), 2.33 (s, 3 H), 2.57 (s, 3 H), 2.65 (s, 3 H), 3.73 (s, 3 H), 3.85 (s, 3 H), 3.95 (s, 3 H), 4.33 (q, J = 7 Hz, 2 H); mass spectrum, m/e (M^+) 333. Anal. Calcd for $C_{18}H_{23}NO_5$: C, 64.88; H, 6.95; N, 4.20. Found: C, 64.88; H, 7.06; N, 4.23.

Ethyl 4-Acetamino-5,7-dimethoxy-1,2,6-trimethyl-3-indolecarboxylate (16a). To a solution of **14a** (614 mg, 1.84 mmol) in 8 mL of ethanol and 8 mL of pyridine was added 1.28 g (18.4 mmol) of hydroxylamine hydrochloride. The reaction mixture was stirred at reflux overnight, concentrated, and partitioned between ether and H_2O. The organic phase was dried over $MgSO_4$ and concentrated to give 491 mg of crude oxime. This was dissolved in 15 mL of dry benzene, and 0.50 g of phosphorus pentachloride was added. After being stirred at room temperature for 5 min, the reaction mixture was quenched with H_2O and $NaHCO_3$ solution and extracted with ether. The ether solution was washed with saturated NaCl and dried over $MgSO_4$. Chromatography using benzene–ether (1:1) and then ethyl acetate as eluent gave 310 mg (48% overall) of a white solid: mp 134–136 °C (ether and petroleum ether); IR ($CHCl_3$) 3285, 1662 cm^{-1}; NMR ($CDCl_3$) δ 1.38 (t, J = 7 Hz, 3 H), 2.09 (s, 3 H), 2.32 (s, 3 H), 2.58 (s, 3 H), 3.76 (2s, 6 H), 3.88 (s, 3 H), 4.40 (q, J = 7 Hz, 2 H), 9.33 (br s, 1 H).

Ethyl 4-Amino-5,7-dimethoxy-1,2,6-trimethyl-3-indolecarboxylate (16b). To a solution of **15a** (56 mg, 0.16 mmol) in 4 mL of absolute EtOH was added 0.1 mL of concentrated HCl. The reaction mixture was stirred at reflux for 24 h, cooled, concentrated, and partitioned between ether and $NaHCO_3$ solution. The organic phase was washed with H_2O three times, dried over $MgSO_4$, and concentrated. Chromatography with benzene–ether (1:1) as eluent gave 37 mg (75%) of a yellow solid: mp 126–128 °C (from EtOH); IR ($CHCl_3$) 3450, 3318, 1676 cm^{-1}; NMR ($CDCl_3$) δ 1.38 (t, J = 7 Hz, 3 H), 2.32 (s, 3 H), 2.57 (s, 3 H), 3.73 (2s, 6 H), 3.91 (s, 3 H), 4.38 (q, J = 7 Hz, 2 H), 5.61 (br s, 2 H). Anal. Calcd for $C_{16}H_{22}N_2O_4$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.72; H, 7.38; N, 8.89.

Ethyl 5-Methoxy-1,2,6-trimethyl-4,7-dioxo-3-indolecarboxylate (1a). To a solution of **15b** (34 mg, 0.11 mmol) in 2 mL of dry THF was added 45 mg of argentic oxide (0.36 mmol) followed by 0.1 mL of 6 N HNO_3. After being stirred for 5 min at 0 °C, the reaction mixture was concentrated and partitioned between chloroform and sodium bicarbonate solution. The chloroform phase was washed with H_2O, dried over $MgSO_4$, and concentrated. The crude product was subjected to preparative TLC using benzene–ether (8:1) to give a reddish yellow solid (23 mg) which recrystallized from hexane to give 18 mg (55%) of **1a**: mp 94–95 °C (hexane); IR ($CHCl_3$) 1705, 1671, 1640 cm^{-1}; NMR ($CDCl_3$) δ 1.36 (t, J = 7 Hz, 3 H), 1.95 (s, 3 H), 2.44 (s, 3 H), 3.90 (s, 3 H), 4.03 (s, 3 H), 4.38 (q, J = 7 Hz, 2 H); mass spectrum, m/e (M^+) 291; UV (absolute EtOH)[11] 207, 235, 286, 328 nm (log ϵ 4.99, 4.87, 4.82, 4.43). Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.89; N, 4.80. Found: C, 61.72; H, 6.00; N, 4.64.

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Registry No.—**1a**, 68395-91-5; **2**, 1125-55-9; **4a**, 32561-17-4; **4b**, 69469-82-5; **5**, 69469-83-6; **6a**, 69469-84-7; **6b**, 69469-85-8; **6c**, 69469-86-9; **8a**, 52163-64-1; **8b**, 69469-87-0; **9a**, 69469-88-1; **9a** oxime, 69469-89-2; **9b**, 69469-90-5; **10**, 69469-91-6; **11a**, 69469-92-7; **11b**, 69469-93-8; **11c**, 69469-94-9; **12**, 69469-95-0; **13**, 69469-96-1; **13**, 69469-97-2; **14a**, 69469-98-3; **14b**, 69469-99-4; **15a**, 69470-00-4; **15b**, 69470-01-5; **16a**, 69470-02-6; **16b**, 69470-03-7; isopropenyl methyl ether, 116-11-0; ethyl acetoacetate, 141-97-9.

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Crystal Structure of the Syn-Diaxial Conformer of 2,2-Diphenyl-1,3-dithiane *cis*-1,3-Dioxide

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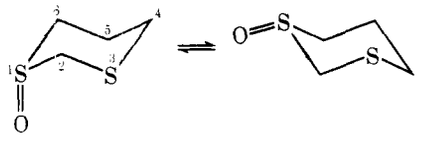
The lower melting 1,3-dioxide of 2,2-diphenyl-1,3-dithiane has been determined to be the cis diastereomer by ^1H and ^{13}C NMR spectroscopy and by single-crystal X-ray diffraction rather than trans as reported in the literature. The molecule exists in the conformation in the crystal which has both sulfoxide oxygens axial in spite of the significant electrostatic repulsions attending this conformation. The preference for the observed conformation appears to result from van der Waals interactions involving the two C(2)-phenyl substituents with each other and with the two oxygens. Crystals of the dioxide conform to space group $P2_1/n$, with a = 9.635 (2), b = 10.096 (3), c = 14.798 (4) Å, β = 98.86 (1)°, and Z = 4. The structure was solved by direct methods, and least-squares refinement gave R = 0.052 for 1680 independent significant reflections measured by counter diffractometry.

Our understanding of the factors which influence the conformational equilibrium in 1,3-dithiane 1-oxide (1) (eq 1) has

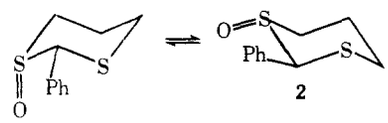


(1)

1

ΔG°_{192} = −0.63 kcal/mol in $CHClF_2$

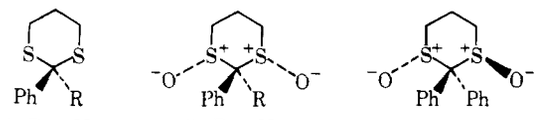
been aided by the systematic examination of the structural features of suitably substituted model compounds as revealed by X-ray crystallography.[1,2] For example, the S(1)–C(2)–S(3) angle is significantly smaller (109.6° vs. 112.9°) in *trans*-2-phenyl-1,3-dithiane 1-oxide (**2**) than in the cis diastereomer **3**, and this angle is smaller in both oxides than in the parent 2-phenyl-1,3-dithiane **4** (114.9°). We have attributed the bond angle contraction in the oxides to an electrostatic attraction between the positively polarized sulfoxide sulfur and S(3). This attraction is opposed in the axial oxide by a repulsive electrostatic interaction between oxygen and S(3), leading to a larger S(1)–C(2)–S(3) angle than in the equatorial oxide.[3] An axial orientation of the sulfoxide group has been observed to be less stable than an equatorial one both in the conformational equilibrium of 1,3-dithiane 1-oxide (eq 1)[4] and in the base-catalyzed equilibration of **2** and **3** (eq 2).[5]



(2)

3 2

ΔG°_{238} = −1.34 kcal/mol in CH_3OH



4, R = H; **6**, R = Ph **5**, R = H; **7**, R = Ph **8**

The C(2) endocyclic angle responds in a predictable fashion toward introduction of a second sulfoxide oxygen. The S(1)···S(3) interaction becomes repulsive since both sulfurs are positively polarized, and the S(1)–C(2)–S(3) angle is observed to be 114.2° in the *cis*-1,3-dioxide (**5**) of 2-phenyl-1,3-dithiane.[1] We have extended our examination of 1,3-dioxides to include a 2,2-disubstituted derivative, thinking that the combination of a crowded environment and the proximity of like dipoles might cause the most stable conformation to be other than a chair. A crystal structure determination could then provide useful information concerning the distortion modes available to oxides of 1,3-dithiane. As will be seen in this paper, the conformation adopted by *cis*-2,2-diphenyl-1,3-dithiane 1,3-dioxide in the crystal was, in fact, a chair, but not the one expected on the basis of electrostatic considerations.

Results and Discussion

The formation of *cis*- (**7**) and *trans*-2,2-diphenyl-1,3-dithiane 1,3-dioxide (**8**) in approximately equal amounts on oxidation of 2,2-diphenyl-1,3-dithiane (**6**) with 2 equiv of hydrogen peroxide in acetic acid has been described by Neugebauer in collaboration with Kuhn[6] and with Otting.[7] Based on its infrared spectrum, the higher melting diastereomer (mp 189 °C) was assigned the cis stereochemistry **7** and the lower melting one (mp 177 °C) the trans structure **8**.[7] On repeating this work, we were able to obtain crystals suitable for X-ray work of one of the isomers much more easily than the other and directed our attention to that diastereomer. It melted at 173–175 °C and had an infrared spectrum identical with that reported for the *trans*-dioxide **8**. Both ^1H and ^{13}C NMR spectroscopy, however, indicated that the structural assignment in the literature was incorrect and that this compound was the *cis*-1,3-dioxide **7**. In addition to multiplets for the four methylene protons at C(4) and C(6), the ^1H NMR spectrum exhibited separate one-proton multiplets centered at 1.9 and 2.8 ppm for the two C(5) protons. This is consistent with the *cis*-1,3-dioxide **7** where the C(5) protons are diastereotopic, but not with the *trans*-1,3-dioxide **8** where the C(5) protons are equivalent on the NMR time scale. Similarly, the ^{13}C NMR spectrum contained six identifiable signals for aromatic carbons in the range 128–136 ppm. Because the phenyl groups are equivalent in the *trans*-1,3-dioxide **8** only four signals are possible for this compound, while the *cis*-1,3-dioxide **7** could

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