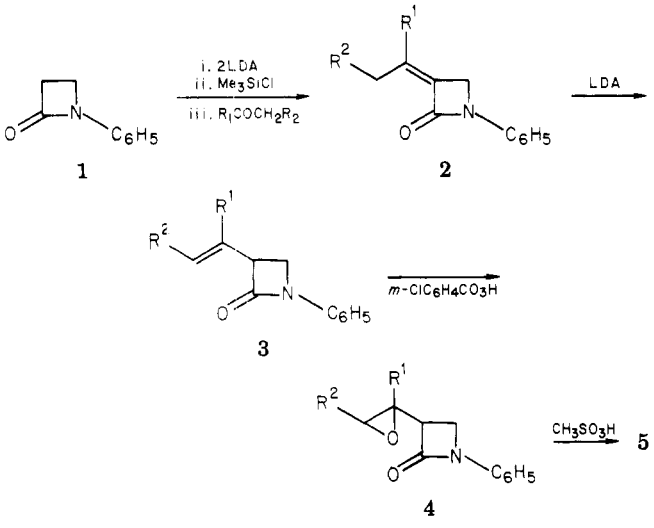
Scheme I



a, $R^1 = CH_3$, $R^2 = H$; b, $R^1 = C_6H_5$, $R^2 = H$; c, R^1, $R^2 = (CH_2)_3$; d, R^1, $R^2 = (CH_2)_4$; e, R^1, $R^2 = (CH_2)_2CH(CH_3)CH_2$; f, R^1, $R^2 = (CH_2)_5$; g, $R^1 = C_6H_5$, $R^2 = CH_3$

Oxidation of 3 with *m*-Chloroperbenzoic Acid. To a solution of **3** (10 mmol) in CH_2Cl_2 (30 mL) was added *m*-chloroperbenzoic acid (1.90 g, 11 mmol), and the mixture was allowed to stir at room temperature for 14 h. The mixture was washed with 5% $NaHCO_3$ solution and water and was dried over Na_2SO_4. Evaporation of the solvent left the corresponding epoxides **4** which gave the specific melting points shown in Table I except for **4g** (oil).

General Procedure for Preparation of α-Anilinomethyl-1,2-butenolides (5). A mixture of CH_3SO_3H (1 mL), benzene (4 mL), and **4** (1 mmol) was heated for 1.5 h under reflux. The mixture was made basic with 28% NH_4OH and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and evaporated to leave **5**. The results are summarized in Table I.

2-(*cis*-2-Hydroxycyclohexyl)propanoic Acid Lactone (6a). A mixture of **5d** (486 mg, 2 mmol), EtOH (25 mL), and prereduced Pt catalyst (300 mg) was shaken under atmospheric pressure of H_2 at 70 °C for 6 h. After removal of the catalyst, the solvent was evaporated. A solution of the resulting residue in benzene (60 mL) was washed with 5% HCl and water and was dried over Na_2SO_4. Evaporation of the solvent gave **6a** (290 mg, 94%), which was identified by comparison of spectral data with those of an authentic specimen.[8]

2-(*cis*-2-Hydroxycycloheptyl)propanoic Acid Lactone (6b). A sample of **5f** (514 mg, 2 mmol) was reduced in the presence of prereduced Pt catalyst (300 mg) as above. The mixture was worked up as above to yield **6b** (309 mg, 92%) as an oil: ^1H NMR ($CDCl_3$) δ 1.16 (d, J = 7.5 Hz, 3 H), 1.15–2.98 (m, 12 H), 4.41–4.80 (m, 1 H); MS m/e 168 (M^+), 166 ($M^+ - 2$), 166.100 65 (calcd for $C_{10}H_{14}O_2$, 166.099 394); IR ($CHCl_3$) ν(C=O) 1715 cm^{-1}.

Reduction of 5d with Raney Ni. A mixture of **5d** (486 mg, 2 mmol), EtOH (35 mL), and Raney Ni catalyst (6 mL) was shaken under atmospheric pressure of H_2 at 70 °C for 6 h. After removal of the catalyst, the solvent was evaporated, and the resulting solid was recrystallized from ether–hexane to give **7a** (460 mg, 95%): mp 94–96.5 °C; ^1H NMR ($CDCl_3$) δ 1.04–1.89 (m, 4 H), 2.15–2.58 (m, 5 H), 3.00 (m, 1 H), 3.38 (d, J = 6 Hz, 1 H), 3.45 (d, J = 6 Hz, 1 H), 4.44 (m, 1 H), 6.59–7.29 (m, 5 H); MS m/e 245 (M^+). Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.50; H, 7.72; N, 5.53.

Reduction of 5f with Raney Ni. A mixture of **5f** (514 mg, 2 mmol), EtOH (40 mL), and Raney Ni catalyst (7 mL) was shaken under atmospheric pressure of H_2 and worked up as above to give **7b** (502 mg, 80%): MS m/e 259 (M^+); ^1H NMR ($CDCl_3$) 1.14–2.85 (m, 11 H), 3.00 (m, 1 H), 3.37 (d, J = 8 Hz, 2 H), 4.62 (m, 1 H), 6.70–7.26 (m, 5 H). Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.28; H, 8.33; N, 5.21.

2-(*cis*-2-Hydroxycyclohexyl)propenoic Acid Lactone (10d). A mixture of **7a** (500 mg, 2.06 mmol), methyl iodide (2 mL), and MeOH (10 mL) was heated for 5 h under reflux. The solvent was evaporated, and the resulting residue was made basic with 28% NH_4OH and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and evaporated to leave **8a** (470 mg, 88%); this was further methylated, without purification, with methyl iodide (2 mL) in MeOH under reflux for 5 h. The solvent was evaporated, and the remaining residue was heated in EtOH (10 mL) in the presence of EtONa (150 mg) under reflux for 2 h. The solvent was evaporated, and the resulting residue was extracted with benzene. The extract was washed with 5% HCl (20 mL) and water and dried over Na_2SO_4. Removal of the solvent afforded **10a** (125 mg, 40%), the spectral data of which were identical with those of the authentic specimen.[10]

2-(*cis*-2-Hydroxycycloheptyl)propenoic Acid Lactone (10b). A mixture of **7b** (500 mg, 1.9 mmol), methyl iodide (2 mL), and MeOH (10 mL) was heated and worked up as above to yield **8b** (415 mg, 85%); this was further methylated with methyl iodide (2 mL) in MeOH (10 mL) as above. The remaining residue, obtained on evaporation of the solvent, was heated with EtONa (150 mg) in EtOH (10 mL) for 2 h. The solvent was evaporated, and the resulting residue was extracted with benzene. The extract was washed with 5% HCl and water and dried over Na_2SO_4. Removal of the solvent yielded **10b** (141 mg, 45%), the spectroscopic data of which were identical with those of the authentic specimen:[10] MS m/e 166.098 371 (M^+) (calcd for $C_{10}H_{14}O_2$) m/e 166.099 364).

Registry No. 1, 5099-95-6; **2a**, 68695-52-3; **2b**, 68695-57-8; **2c**, 68695-53-4; **2d**, 68695-54-5; **2e**, 68695-55-6; **2f**, 71250-55-0; **2g**, 71250-56-1; **3a**, 71250-57-2; **3b**, 71250-58-3; **3c**, 71250-59-4; **3d**, 71250-60-7; **3e**, 71250-61-8; **3f**, 71250-62-9; (*E*)-**3g**, 71250-63-0; (*Z*)-**3g**, 71250-64-1; **4a**, 71250-65-2; **4b**, 71250-66-3; **4c**, 71250-67-4; **4d**, 71250-68-5; **4e**, 71250-69-6; **4f**, 71250-70-9; **4g**, 71250-71-0; **5a**, 71250-72-1; **5b**, 71250-73-2; **5c**, 71250-74-3; **5d**, 71250-75-4; **5e**, 71250-76-5; **5f**, 71250-77-6; **5g**, 71250-78-7; **6a**, 2205-25-6; **6b**, 33366-33-5; **7a**, 71250-79-8; **7b**, 71250-80-1; **8a**, 71250-81-2; **8b**, 71250-82-3; **10a**, 16822-06-3; **10b**, 3725-04-0; methyl iodide, 74-88-4; propanone, 67-64-1; acetylbenzene, 98-86-2; cyclopentanone, 120-92-3; cyclohexanone, 108-94-1; 4-methylcyclohexanone, 589-92-4; cycloheptanone, 502-42-1; 1-phenylpropanone, 93-55-0.

Synthesis of Isotubaic Acid (Rotenic Acid)

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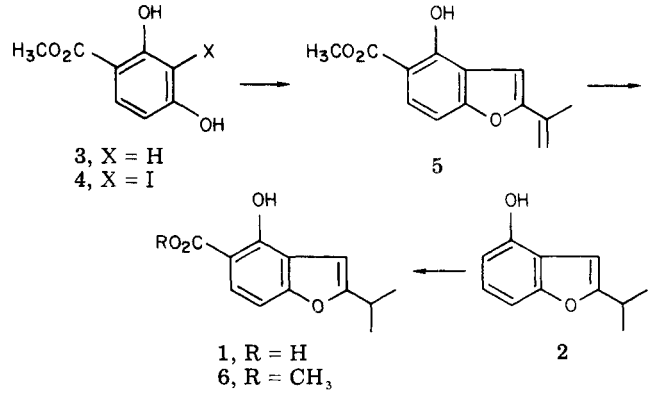
Isotubaic acid (rotenic acid) was first obtained from the natural insecticide rotenone as a significant degradation product. Extensive investigations, which have been reviewed,[1] led to proposed structure 1. By an unusual



(1) F. B. LaForge, H. L. Haller, and L. E. Smith, *Chem. Rev.*, 12, 181 (1933).

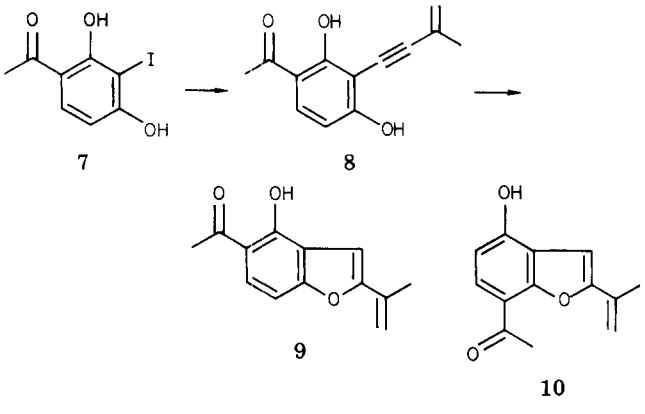
0022-3263/79/1944-3948$01.00/0

synthesis of this benzofuran, starting from 2-isopropylfuran, Reichstein et al.[2] provided confirmation, and subsequent syntheses were reported by Shriner et al.[3] and Shamshurin.[4] Each of these three procedures, in addition to being lengthy, gave in the penultimate step the benzofuranol isotubanol (2) which was finally carboxylated by the Kolbe–Schmitt procedure. We report here a notably brief synthesis, differing conceptually in that the required carboxylate function is initially present and is retained.

Construction of the benzofuran nucleus by reaction of an *o*-halophenol with a cuprous acetylide[5] has been utilized in the synthesis of several natural products which are derivatives of 2-isopropylbenzofuran.[6-10] The present investigation was undertaken partly to ascertain the applicability of such acetylide coupling to a 2-haloresorcinol. The desired starting iodoresorcinol (4) was readily obtained by addition of iodine to methyl 2,4-dihydroxybenzoate (3) in aqueous ethanol containing potassium iodate. The ^1H NMR spectrum of the readily isolated product confirmed that monosubstitution had occurred at C-3. Treatment of 4 with cuprous isopropenylacetylide in the usual way yielded methyl 4-hydroxy-2-isopropenylbenzofuran-5-carboxylate (5) in 38% yield.

Catalytic hydrogenation of this isopropenylbenzofuran with palladium–carbon cleanly afforded the methyl ester 6, which on base hydrolysis gave isotubaic acid (1). The melting points of both acid and ester were in excellent agreement with those previously reported, and the ^1H NMR spectra were fully consistent.

In a preliminary experiment, the action of cuprous isopropenylacetylide on the known and readily available iodoacetophenone[11] (7) was examined. It was hoped that



this reaction, in addition to indicating the feasibility of the coupling, would establish that the para hydroxyl function would be involved in addition to the presumed arylacetylide intermediate 8 to give 9, rather than the ortho hydroxyl function to give 10. Since the benzofuran product, isolated in 42% yield, retained the spectroscopic characteristics of an *o*-hydroxyaryl ketone, the essential validity of the approach was vindicated.

Experimental Section

Methyl 2,4-Dihydroxy-3-iodobenzoate (4). A solution of methyl 2,4-dihydroxybenzoate (3; 5.0 g) in warm ethanol was added to iodine (3.02 g) and potassium iodate (1.27 g) in water (ca. 40 mL) and the mixture stirred at room temperature for 1.5 h, after which the iodine color had disappeared. The accumulated precipitate was collected, washed with water, and crystallized from acetic acid as needles (2.30 g): mp 145–146 °C; ^1H NMR [$(CD_3)_2CO$] δ 3.92 (s, CO_2Me), 6.58 (d, J = 6 Hz, H-5), 7.72 (d, J = 6 Hz, H-6).

Anal. Calcd for $C_8H_7O_4I$: C, 32.67; H, 2.40. Found: C, 32.54; H, 2.49.

The presence of some 3,5-diiodobenzoate in the crude precipitate was indicated in the ^1H NMR spectrum.

Methyl 4-Hydroxy-2-isopropenylbenzofuran-5-carboxylate (5). To a suspension of cuprous isopropenylacetylide[6] (3.29 g) in pyridine (150 mL) was added a solution of the iodo ester 4 (7.06 g) in the same solvent (150 mL) and the mixture heated under reflux (nitrogen atmosphere) for 22 h. It was then cooled, diluted with ether (1500 mL), set aside at 0 °C overnight, and filtered. The filtrate was washed with brine and water, treated with charcoal, dried ($MgSO_4$), and evaporated. A solution of the residue in benzene was filtered through a short column of silica gel, and the colorless eluate crystallized from methanol to give the isopropenylbenzofuran 5 as needles (2.15 g): mp 108–108.5 °C; ^1H NMR ($CDCl_3$) δ 2.12 (d, J = 1 Hz, MeC=C), 3.95 (s, CO_2Me), 5.17 (m, vinylic H), 5.75 (br s, vinylic H), 6.81 (br s, H-3), 6.97 (dd, J = 9 and 1 Hz, H-7), 7.74 (d, J = 9 Hz, H-6), 11.08 (s, OH).

Anal. Calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 67.45; H, 5.46.

Methyl 4-Hydroxy-2-isopropylbenzofuran-5-carboxylate (6). A solution of the isopropenylbenzofuran 5 (144 mg) in ethyl acetate (15 mL) was stirred with palladium–carbon (5%, 140 mg) under hydrogen at atmospheric pressure overnight (gas uptake essentially complete after 3 h). Removal of the catalyst and solvent and crystallization of the residue from methanol gave isotubaic acid methyl ester (6) as needles (120 mg): mp 39–39.5 °C (lit.[12] mp 39–40 °C); ^1H NMR ($CDCl_3$) δ 1.34 (d, J = 7 Hz, $CHMe_2$), 3.06 (septet, J = 7 Hz, $CHMe_2$), 3.95 (s, CO_2Me), 6.56 (br s, H-3), 6.95 (dd, J = 9 and 1 Hz, H-7), 7.69 (d, J = 9 Hz, H-6), 11.35 (s, OH).

4-Hydroxy-2-isopropylfuran-5-carboxylic Acid (1). Saponification of the methyl ester 6 in the usual way give isotubaic acid (rotenic acid) as fine crystals from benzene: mp 185 °C (lit.[13] mp 185 °C); ^1H NMR [$(CD_3)_2CO$] δ 1.30 (d, J = 7 Hz, $CHMe_2$), 3.06 (septet, J = 7 Hz, $CHMe_2$), 6.56 (br s, H-3), 6.99 (dd, J = 9 and 1 Hz, H-7), 7.73 (d, J = 9 Hz, H-6).

2,4-Dihydroxy-3-iodoacetophenone (7). 2,4-Dihydroxyacetophenone (10 g) was treated with iodine (6.67 g) and potassium iodate (2.81 g), as for 4. Crystallization of the precipitate (11.61 g) from acetic acid gave the iodoacetophenone 7: mp 168–169 °C (lit.[11] mp 164 °C); ^1H NMR [$(CD_3)_2CO$] δ 2.58 (s, COMe), 6.59 (d, J = 6 Hz, H-5), 7.77 (d, J = 6 Hz, H-5), 13.78 (s, OH).

5-Acetyl-4-hydroxy-2-isopropenylbenzofuran (9). A solution of the iodoacetophenone 7 (1.39 g) in pyridine (50 mL) was reacted with cuprous isopropenylacetylide (0.68 g) in pyridine (50 mL), and the mixture was worked up as for 5. Crystallization of the product from methanol gave the isopropenylbenzofuran 9 as yellow needles (42% yield): mp 114–115 °C; ^1H NMR ($CDCl_3$) δ 2.11 (s, MeC=C), 2.64 (s, COMe), 5.18 (br s, vinyl H), 5.74 (s, vinyl H), 6.82 (s, H-3), 6.97 (d, J = 9 Hz, H-7), 7.62 (d, J = 9 Hz, H-6), 12.63 (s, intermolecular H-bonded OH).

Anal. Calcd for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 72.45; H, 5.93.

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Registry No. 1, 526-49-8; 3, 2150-47-2; 4, 71243-09-9; 5, 71243-10-2; 6, 71243-11-3; 7, 71243-12-4; 9, 71243-13-5; cuprous isopropenylacetylide, 56964-06-8; 2,4-dihydroxyacetophenone, 89-84-9.

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