Natural Benzofurans: Synthesis of Isopterofuran

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A synthesis of the fungistatic phytoalexin, isopterofuran is described. In the key step, the benzofuran heterocycle is constructed by reaction of an *o*-iodophenol with a cuprous arylacetylide.

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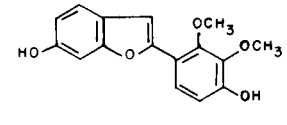
From the leaflets of scorpion senna, *Coronilla emerus* inoculated with *Helminthosporium carbonum,* there has been isolated a benzofuran phytoalexin, which was identified as 2-(4-hydroxy-2,3-dimethoxyphenyl)-6-hydroxybenzofuran (**1**) and named isopterofuran (1). We report here a synthesis of this product based upon benzofuran formation by reaction of an appropriate *o*-halogenophenol (or ester) with a cuprous acetylide, a procedure we have used previously for the synthesis *inter alia* of the related pterofuran (**2**)(2) and medicagol methoxybenzofuran (**3**)(3).

The required acetylene was readily prepared from 2,3,4-trihydroxyacetophenone which was first benzylated to yield the 4-benzyl ether derivative (**4**) (4), then methylated by a standard method to give 4-benzyloxy-2,3-dimethoxyacetophenone (**5**). This ketone was converted to the hydrazone **6**, which on treatment with iodine in the presence of triethylamine gave the vinyl iodide **7**. Elimination of hydrogen iodide from **7** was effected by treatment with sodium hydride to give 4-benzyloxy-2,3-dimethoxyphenylacetylene (**8**). This methyl ketone → alkyne preparation is based upon a procedure developed by Oliveto (5) and Barton (6) and their coworkers. The cuprous acetylide (**9**) was generated in the standard manner (7) with cupric sulphate and hydroxylamine hydrochloride in aqueous ammonium hydroxide.

An initial attempt to form the benzofuran heterocycle by reaction of **9** with the commercially available 4-bromoresorcinol was unsuccessful with 1,4-*bis*(4-benzyloxy-2,3-dimethoxyphenyl)buta-1,3-diyne (**10**) being the major product. A similar attempt by reaction of the bromophenol with the alkyne **8** and activated copper powder (8) was also unsuccessful.



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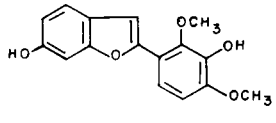

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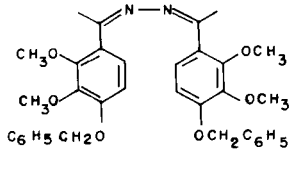

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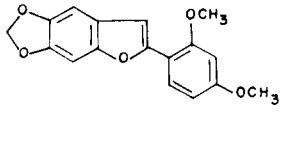

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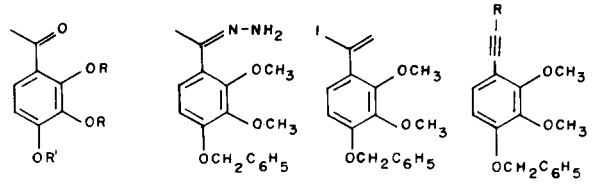
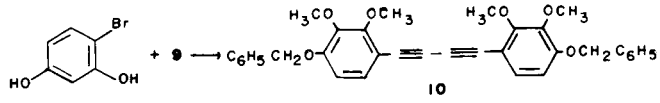


4 R = H, R' = $CH_2C_6H_5$ **5** R = CH_3, R' = $CH_2C_6H_5$ **6** **7** **8** R = H **9** R = Cu

Benzofuran formation was successful, however, by reaction of **9** with 6-iodoresorcinol 3-benzoate (**11**) (2,9) to give in good yield the arylbenzofuranol benzoate ester **12**. This was converted to isopterofuran (**1**) in two steps by ester hydrolysis with lithium aluminium hydride followed by debenzylation by catalytic hydrogenolysis. The spectroscopic properties of isopterofuran and the diacetate derivative were in excellent agreement with those reported.



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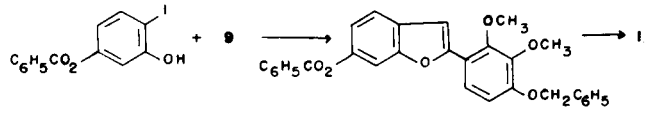

11 **12**

EXPERIMENTAL

Nmr spectra were determined for solutions in deuteriochloroform with tetramethylsilane as internal standard.

4-Benzyloxy-2,3-dihydroxyacetophenone (**4**).

This compound was prepared as described (4) with mp 137-138.5°; nmr: δ 2.55 (s, Me), 5.26 (s, $PhCH_2O$), 5.57 (s, 3-OH), 6.56 (d, J = 9 Hz, H-5), 7.29 (d, J = 9 Hz, H-6), 7.42 (br. s, ArH) and 12.56 (s, 2-OH).

4-Benzyloxy-2,3-dimethoxyacetophenone (**5**).

To a stirred mixture of the catechol **4** (6.64 g) and potassium carbonate (23 g) in acetone (110 ml) was added a solution of dimethyl sulphate (6.65 g) in acetone (25 ml) dropwise over 20 minutes. The mixture was then heated under reflux for 17 hours, filtered and the solvent removed under reduced pressure to yield an oil which was dissolved in ether and washed successively with water (3 × 100 ml), aqueous sodium hydroxide (0•1N, 3 × 50 ml), saturated brine (3 × 100 ml) and water. Evaporation of the dried (sodium sulfate) extract gave an orange semi-

solid which was distilled (kugelrohr, 0.5 mm, 177-182° bath temperature) to give **5** as a colourless oil (5.47 g); nmr: δ 2.55 (s, COMe), 3.87 (s, OMe), 3.95 (s, OMe), 5.14 (s, $PhCH_2O$) 6.77 (d, J = 9 Hz, H-5), 7.37-7.43 (m, ArH) and 7.52 (d, J = 9 Hz, H-6).

Anal. Calcd. for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.48; H, 6.29.

4-Benzyloxy-2,3-dimethoxyacetophenone Hydrazone (**6**).

Hydrazine (95%, 6 ml) was added to a solution of the ketone **5** (5.46 g) in ethanol (100 ml) and triethylamine (50 ml) and heated under reflux for 4 hours and kept overnight at room temperature. It was then diluted with water, extracted with ether and worked up in the usual way to give the hydrazone **6** as a yellow oily solid; nmr: δ 2.08 (s, Me), 3.87 (s, OMe), 3.91 (s, OMe), 5.11 (s, $PhCH_2O$), 5.34 (br. s, $-NH_2$), 6.72 (d, J = 9 Hz, H-5), 7.06 (d, J = 9 Hz, H-6) and 7.42 (m, ArH). Attempted crystallization of the hydrazone from ethanol resulted in the conversion to 4-benzyloxy-2,3-dimethoxyacetophenone azine (**13**) (10) mp 108-109; nmr: δ 2.22 (s, (Me), 3.93 (s, 2- and 3-OMe), 5.16 (s, $PhCH_2O$), 6.74 (d, J = 9 Hz, H-5), 7.22 (d, J = 9Hz, H-6) and 7.35-7.42 (m, ArH); ms: Calcd. M^+ (m/e 568). Found m/e 568 (M^+), 538 (M^+ -30), 269 (ArCMe = N • -Me).

Anal. Calcd. for $C_{34}H_{36}O_6N_2$: C, 71.81; H, 6.38; N, 4.93. Found: C, 71.96; H, 6.50; N, 4.83.

4-Benzyloxy-2,3-dimethoxyphenylacetylene (**8**).

To a stirred solution of the hydrazone **6** (4.57 g) in tetrahydrofuran (300 ml) and triethylamine (136 ml), was added dropwise over 40 minutes under nitrogen a solution of iodine (11.14 g) in tetrahydrofuran (30 ml). Stirring was continued for 1.5 hours, then the mixture diluted with water (200 ml) and extracted with ether (3 × 100 ml). Successive washing of the extract with 1*N* hydrochloric acid, saturated sodium bicarbonate solution, 10% sodium thiosulfate, brine and evaporation after drying (sodium sulfate) gave the crude vinyl iodide **7** as a black oil (5.87 g); nmr: δ 3.89 (s, OMe), 3.97 (s, OMe), 5.11 (s, $PhCH_2O$), 6.12 (br. s, vinyl H), 6.26 (br. s, vinyl H), 6.74 (d, J = 8 Hz, H-5), 6.96 (d, J = 8 Hz, H-6) and 7.27-7.48 (m, ArH). A solution of the vinyl iodide (**7**) (5.87 g) in dry tetrahydrofuran (75 ml) was added to sodium hydride (3.5 g, from a 50% oil dispersion washed with pentane) under nitrogen, and the mixture heated under reflux for 24 hours. The reaction was quenched by addition of ethanol, dilution with water and extraction with ether. Evaporation of the washed and dried extract gave a dark viscous oil which was distilled (kugelrohr, 0.5 mm, 160° bath temperature) to give an amber oil (2.22 g) which crystallized from hexane to give the acetylene **8** as prisms, mp 59-60°; nmr: δ 3.20 (s, alkyne-H), 3.90 (s, OMe), 4.01 (s, OMe), 5.12 (s, $PhCH_2O$), 6.67 (d, J = 8 Hz, H-5), 7.14 (d, J = 8 Hz, H-6) and 7.31-7.48 (m, ArH).

Anal. Calcd. for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.01; H, 6.12.

Cuprous 4-Benzyloxy-2,3-dimethoxyphenylacetylide (**9**).

Hydroxylamine hydrochloride (537 mg) was added portionwise with stirring to a cooled (ice-bath) solution of cupric sulfate pentahydrate (975 mg) in concentrated ammonium hydroxide (4 ml) and water (20 ml) under nitrogen. When the deep blue colour had faded, a solution of the alkyne **8** (1.00 g) in ethanol (25 ml) was added, and the consequent yellow precipitate collected after further dilution with water (25 ml). It was washed with water, ethanol and ether and dried (phosphorus pentoxide) under reduced pressure to give the cuprous acetylide **9** as a yellow powder (1.1 g), mp 171-175 dec°.

Reaction of Acetylide **9** with 4-Bromoresorcinol.

A solution of 4-bromoresorcinol (0.6 g) in pyridine (10 ml) was added to the cuprous acetylide **9** (1.047 g) in the same solvent (30 ml) and the mixture refluxed under nitrogen for 18 hours. It was then cooled, diluted with ether (600 ml), stored overnight at 0° and filtered. The filtrate was washed with water (3 × 100 ml) and brine, dried (sodium sulfate) and evaporated to give a residual red solid (970 mg) which was chromatographed on silica gel. Elution with benzene gave first the acetylene **8** (295 mg) followed by 1,4-*bis*(4-benzyloxy-2,3-dimethoxyphenyl)-buta-1,3-diyne (**10**) (182 mg) obtained by crystallization from methanol as prisms, mp 150-152°; ir (potassium bromide): 2145 cm^{-1} (C≡C); nmr: δ 3.90 (s, OMe), 4.03 (s, OMe), 5.13 (s, $PhCH_2O$), 6.68 (d, J = 8 Hz, H-5), 7.18 (d, J = 8 Hz, H-6) and 7.32-7.48 (m, ArH).

Anal. Calcd. for $C_{34}H_{30}O_6$: C, 76.39; H, 5.66. Found: C, 76.43; H, 5.70.

2-(4-Benzyloxy-2,3-dimethyoxyphenyl)benzofuran-6-ol Benzoate (**12**).

A solution of 6-iodoresorcinol 3-benzoate (**11**) (287 mg) and the cuprous acetylide **9** (273 mg) in pyridine (14 ml) was refluxed under nitrogen for 18 hours, then cooled, diluted with ether (500 ml) and filtered after storage at 0° overnight. Evaporation of the washed and dried filtrate gave a dark solid (490 mg) which was purified by chromatography on silica gel (35 g, 40-140 mesh). Elution with benzene gave the benzoate **12** as elongated prisms (317 mg) from methanol, mp 103.5-104°; nmr: δ 3.95 (s, OMe), 4.00 (s, OMe), 5.17 ($PhCH_2O$), 6.82 (d, J = 8.5 Hz, H-6'), 7.08 (dd, J = 2.1 and 8.5 Hz, H-5), 7.24 (s, H-3), 7.31-7.69 (m, H-4, 7 and 5', and eight ArH) and 8.19-8.29 (m, H-2 and 6 of -OCOPh).

Anal. Calcd. for $C_{30}H_{24}O_6$; C, 74.99; H, 5.03. Found: C, 74.73; H, 5.25.

2-(4-Hydroxy-2,3-dimethoxyphenyl)-6-hydroxybenzofuran (Isopterofuran) (**1**).

A solution of the benzoate **12** (542 mg) in ether (40 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (320 mg) in ether (19 ml) and the mixture refluxed for 1.5 hours. Work up in the usual way, and purification of the product by chromatography on silica gel and elution by chloroform to give isopterofuran benzyl ether as an oil (344 mg); nmr: δ 3.94 (s, OMe) 3.95 (s, OMe), 4.68 (s, OH), 5.12 (s, $PhCH_2O$) 6.74 (dd, J = 2 and 8 Hz, H-5), 6.77 (d, J = 9 Hz, H-5'), 6.96 (br. d, J = 2 Hz, H-7), 7.14 (d, J = 1 Hz, H-3), 7.32-7.41 (m, ArH and H-4) and 7.58 (d, J = 9 Hz, H-6').

A solution of the benzyl ether (140 mg) in acetic acid (15 ml) was stirred with palladium-carbon (10%, 46 mg) under hydrogen at atmospheric pressure for 45 minutes. Removal of catalyst and solvent gave isopterofuran (**1**) as an oil (96 mg); nmr: δ 3.92 (s, OMe), 3.97 (s, OMe), 5.95 (br. s, OH), 6.76 (dd, J = 2 and 8 Hz, H-5), 6.80 (d, J = 9 Hz, H-5'), 6.99 (d, J = 2 Hz, H-7), 7.09 (d, J = 1 Hz, H-3), 7.38 (d, J = 8 Hz, H-4), and 7.58 (d, J = 9 Hz, H-6').

Isopterofuran Diacetate.

This derivative was obtained by acetylation with acetic anhydride and pyridine at room temperature overnight. Crystallization from aqueous methanol gave the diacetate as prisms, mp 112-113° (lit (1) mp 113-114°); nmr: δ 2.34 (s, OAc), 2.35 (s, OAc), 3.92 (s, OMe), 3.95 (s, OMe), 6.93 (d, J = 8.5 Hz, H-5'), 6.98 (dd, J = 8.5 and 2 Hz, H-5), 7.30 (br. s, H-3 and 7), 7.56 (d, J = 8.5 Hz, H-4) and 7.71 (d, J = 8.5 Hz, H-6').

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