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CHEMISTRY OF *SAURURUS CERNUUS* III:[1] SOME REACTIONS OF THE DIARYLBUTANE-TYPE NEOLIGNANS

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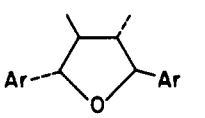
ABSTRACT.—The reaction of austrobailignan-5 (**5**), a 1,4-diarylbutane-type neolignan, and the major lignoid component of *Saururus cernuus*, with dichlorodicyanoquinone was found to yield the corresponding 4-arylnaphthalene (**6**) through cyclization and aromatization of the 4-carbon bridge. The reaction also gave as a by-product, a compound in which one of the methyl groups was oxidized to an aldehyde (**9**). Conditions for the conversion of (±) 2,3-diveratroylbutane exclusively to either (±) veraguensin (**2**) or (±) galbelgin (**1**) are described. Another set of conditions gave a mixture of these two and a third neolignan, saucernetin (**22**), recently isolated from *S. cernuus*.

The isolation of seven lignoids from *Saururus cernuus* and their structural elucidation has been described earlier (1,2). These represent a variety of neolignoid structural types, some novel and some already known. Compounds such as manassantins A and B, which show some degree of neuroleptic activity, contain a central 2,5-*bis*-(4-hydroxy-3-methoxyphenyl)tetrahydrofuran system with each of the phenolic hydroxyls being converted to an arylglycolyl ether. These compounds thus consist of a novel dineolignan skeleton, and a synthesis of such a system must start with the appropriate diaryltetrahydrofuran.

Past syntheses of 2,5-diaryltetrahydrofuranoid neolignans such as galbelgin (**1**) and veraguensin (**2**) were based on radical coupling of phenolic monomers (3-5), and very little effort was devoted to the cyclization of the corresponding diols such as **3**. Details for the stereochemical preference for the formation of **3** from the dione **4** or for the acid-catalyzed cyclization of **3** to the tetrahydrofuran have not been readily available. The current objective is to examine the conditions for the cyclization of a diol such as **3** to either **1** or **2**. Also, because the plant *S. cernuus* contains as the major lignoid component, the known (−)-austrobailignan-5 (**5**) (1,7), a 1,4-diarylbutane-type neolignan, a study of the feasibility of its conversion to a diol such as **3** was made first and is described here.

Functionalization of the two benzylic carbons of **5** with halogen, OH, or C=O groups was studied first using a variety of reagents and conditions. Thus, benzylic



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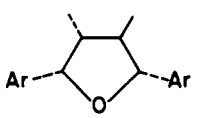

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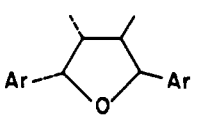

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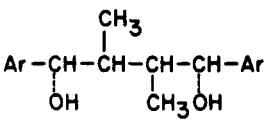

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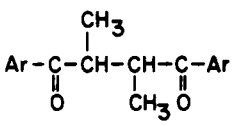


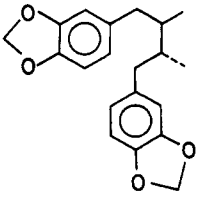
4

Ar=3,4-Dimethoxyphenyl

[1]For Part II, see Rao and Alvarez (2).

bromination of **5** was attempted using *N*-bromosuccinimide (NBS) as well as Br_2, but the reactions yielded mostly the known nuclear bromination product (7). The action of $Pb(OAc)_4$ on **5** in HOAc also gave a mixture of products consisting of phenolic compounds and the corresponding quinonoid substances but none with the desired functionality such as Ar-CH(OH)- or Ar-CH($OCOCH_3$)-.

Several reagents known to convert benzylic methylene to a keto function were, likewise, without effect, i.e., either gave no reaction or gave steady destruction of the compound. However, **5** reacted smoothly with dichlorodicyanoquinone (DDQ) to yield a crystalline product with the molecular formula $C_{20}H_{16}O_4$, as compared with $C_{20}H_{22}O_4$ for **5**. Its uv spectrum showed sharp maxima at 328 and 315 nm, which were absent in **5**, and the relative intensities of the peaks at 285 and 235 nm were also different. The nmr spectrum: δ 2.06, 2.38, s, 3H each; 5.83, 5.96, s, 2H each; 6.50-7.71, m, 6H, clearly showed that the compound had the structure **6** (8), in which the central 4-carbon chain was converted to a cyclic and aromatic system. The product was analogous to the well-known dehydroguaiaretic acid dimethyl ether (**7**) prepared from guaiaretic acid dimethyl ether (**8**) by the action of $Hg(OAc)_2$ and I_2 (Hubl's reagent) by Schroeter *et al.* (9). The reaction of **5** with DDQ also gave a minor product identified as the aldehyde **9**.



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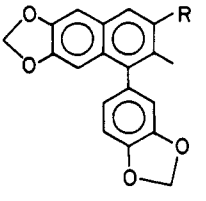
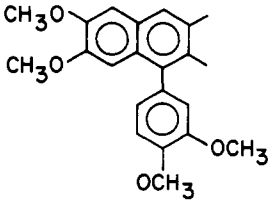


6 R=CH_3
9 R=CHO



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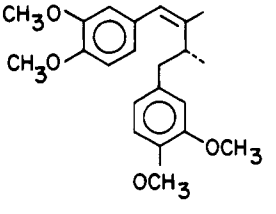

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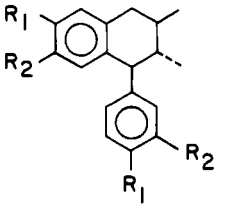
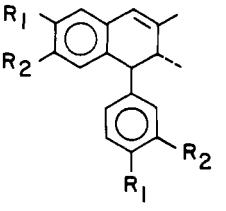
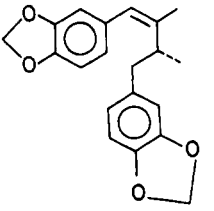
The conversion of **5** to **6** required a minimum of two equivalents of DDQ. With three equivalents and at a temperature of 80-100°, the reaction was essentially complete in 1 h, yielding a 3:1 mixture of **6** and **9**. Among the solvents tried, MeOH, dioxane, and xylene were suitable, but pyridine was not. Conversion of **5** to **6** also proceeded with SeO_2 in HOAc, or NBS in C_6H_6, or $CHCl_3$ in the presence of a sunlamp. In dioxane, however, NBS gave the nuclear bromination product.

To gain additional insight, the course of the reaction with two equivalents of DDQ was followed at 20° by gc analysis. The major product **6** started after 1-2 h and continued to increase, while the aldehyde **9** appeared only after 10-15 h. In addition to these, a series of peaks that might be considered as intermediates were found. Two of these of significant intensity were designated as I_1 and I_2. During the gc-monitoring of the reaction, the concentrations of these intermediates increased until **6** and **9** began to appear and then decreased as **6** and **9** increased. A mixture of these could be separated from the other components, but the two were almost inseparable except by gc or extensive and repeated tlc. When separated in this way on a small scale, I_1 showed a uv spec-

trum nearly identical to that of guaiacin dimethyl ether (**10**) (1), while I_2 showed λ max of 285 nm but with a pronounced shoulder at 310-315 nm. This spectrum was nearly identical to that of cyclogalbelgin (**11**) (1). These spectra together with a gc/ms analysis of I_1/I_2 mixture showed that the two compounds had the structures **12** and **13**, with **12** being the major component. Thus, the reaction did not generate a compound with an unsaturated chain such as **14**, analogous to guaiaretic acid dimethyl ether (**8**). It appears that a carbocation generated by DDQ, instead of undergoing elimination to give **14**, prefers to cyclize to **12**. Further dehydrogenation of **12** to **13** and eventually to **6** have precedents in the literature.



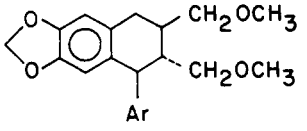


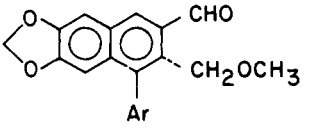


10 $R_1=R_2=OCH_3$
12 $R_1,R_2=OCH_2O$

11 $R_1=R_2=OCH_3$
13 $R_1,R_2=OCH_2O$

14





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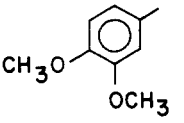
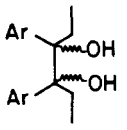


15 **16**

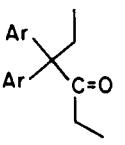
In recent years, a number of publications appeared on the action of DDQ on lignoid compounds (10-12). The most relevant of these deals with the conversion of **15** to **16**, in which a tetrahydronaphthalene was converted to a dihydronaphthalene and subsequently to a naphthalene, and a $-CH_2OCH_3$ group on the side-chain to an aldehyde. In this example **15**, a cyclic system was already present, and dehydrogenation of such a system to a naphthalene is readily accomplished. Even in the case of conversion of **8** to **7**, the 4-carbon chain has a double bond that provides a focus for attack. In contrast to both these examples, in the present case of **5**, a fully saturated 4-carbon chain has been cyclized and aromatized to give **6**. Formation of the minor product **9** either from **13** or **6** is in line with that reported by Ward *et al.* (10), although in the present case a CH_3 group instead of a CH_2OCH_3 group has been oxidized to an aldehyde.

Because **5** could not be converted to a diol, the alternative diol **3** was prepared by synthesis from **4**, which was obtained by the coupling of 3,4-dimethoxypropiophenone and 2′-bromo-3,4-dimethoxypropiophenone in liquid NH_3 and Na (6,13). This reaction gave, besides the expected dione **4**, a crystalline by-product for which the structure **17** was assigned. When treated with an acid, **17** rearranged to the ketone **18** (ν 1700 cm^{-1}, *m/z* 372, 315). Oxidation of **17** with periodate yielded 3,4-dimethoxypropiophenone.

Reduction of the diketone **4** by LAH gave the diol **3** (6). Alternate reduction of the diketone **4** with $NaBH_4$ gave, as the major product, the hydroxytetrahydrofuran **19**. Its structure was confirmed by its ready conversion to **20** in the presence of acid, or Ac_2O and pyridine, and to the furan **21** by treatment with Pd/C. Catalytic hydrogenation of **20** gave veraguensin (**2**) as the sole product. Although Biftu *et al.* (6) prepared veraguensin from **4** by direct catalytic reduction with a low catalyst/substrate ratio, this reduction has been found to be very slow and yields a mixture of products.



17



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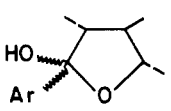

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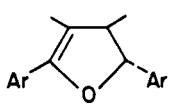

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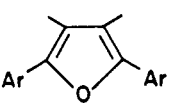

21

Ar=3,4-Dimethoxyphenyl

Cyclization of the diol **3** was studied under a variety of conditions: BF_3 or CF_3CO_2H in C_6H_6; HOAc (neat) or 1% HOAc in $CHCl_3$ with a sun lamp, no reaction occurring without the sun lamp; sulfonic acid type resin; $CuBr_2$ in EtOAc; and heating at 150° in oxydiethanol. When the products were analyzed by gc, galbelgin (**1**) was found to be the almost exclusive product. Previously, Biftu *et al.* (6) subjected the diol **3** to catalytyic hydrogenation and isolated a mixture of galbelgin (**1**) and galbulin (a phenyltetralin similar to **10**). The present method yields galbelgin (**1**) as the exclusive product. An attempted preparation of the bismethanesulfonate of the diol **3** to study cyclization by displacement, instead, gave a mixture of the tetrahydrofurans: **1, 2,** and saucernetin (**22**) in a ratio of 6:3:1.

Thus, the acid-catalyzed cyclization of the diol **3** leads to galbelgin (**1**) as the exclusive product in high yields. There is a minor possibility of inversion if the displacement route is used, leading also to veraguensin (**2**) or, to a lesser extent, saucernetin (**22**). Conversion of the dione **4** exclusively to veraguensin (**2**) is accomplished readily via **20** and **21** in high yields.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Melting points were determined on a Fisher-Johns apparatus and are uncorrected. The following conditions and instrumentation were used for obtaining the spectra described: uv, EtOH, Beckman 35; ir, KBr pellet, Beckman Acculab 3; nmr, $CDCl_3$ unless otherwise specified, Varian T-60 with TMS as internal standard; and ms, Hitachi Perkin-Elmer RMU-6E. Column chromatography was carried out using silica gel (Merck <0.063 mm); tlc on silica gel (Fisher, H-60 P254,366); and gc on a Varian 2100 gas-chromatograph with a column packing at OV-225 and temperature of 240-260°.

CONVERSION OF **5** TO **6** AND **9**.—A solution of **5** (0.33 g) in dioxane (15 ml) was boiled under reflux with DDQ (1 g, 3 eq) for 1 h. The cooled and filtered reaction mixture was diluted with C_6H_6 and washed successively with aqueous 5% $NaHSO_3$, 0.5 N NaOH, and H_2O. The solvent layer was concentrated to near dryness, and the solid crystallized from Et_2O-C_6H_{14} (1:3) to yield **6** as colorless needles, mp 175°; yield, 0.21 g (65%); ms *m/z* 320 (100), 275 (4), 247 (4), 202 (6), 189 (9), 145 (3), 116 (4), 101 (6). *Anal.* calcd. for $C_{20}H_{16}O_4$: C, 74.99; H, 5.03, Found: C, 75.22; H, 5.11.

The filtrate from **6** was concentrated and purified by preparative tlc (silica gel, C_6H_6-C_6H_{14}, 1:1). The lower Rf compound was recovered and crystallized from MeOH, mp 165°; yield, 0.07 g, 22%; uv λ max 260, 310 nm; ir 1690 cm^{-1}; ^1H nmr δ 2.5, s, 3H (CH_3); 6.02, s, 4H (OCH_2O); 6.73-7.33, m, 6H (arom. H); 8.15, s, 1H (CH=O); ms *m/z* 334. *Anal.* calcd. for $C_{20}H_{14}O_5$: C, 71.85; H, 4.22, Found, C, 71.69; H, 4.35.

Alternatively, a solution of **5** (0.33 g) in HOAc (5 ml) was boiled under reflux with SeO_2 (0.3 g) for 6 h. The cooled and filtered reaction mixture was processed as with **6**, and the product purified by preparative tlc (1:1, C_6H_6-C_6H_{14}). The major band gave a crystalline solid, identical with **6**.

A solution of **5** (0.33 g) in C_6H_6 was stirred with NBS (0.5 g) at 80° and in the presence of a sunlamp. After 3 h, the mixture was processed as described for **6**. Preparative tlc (1:1 C_6H_6-C_6H_{14}) gave two major bands. The faster band gave a crystalline solid, mp 95°, identical with dibromo **5** (7). The slower band, mp 175° was identical with **6**.

3,4-*BIS*(3,4-DIMETHOXYPHENYL)HEXANE-3,4-DIOL (**17**).—Condensation of 3,4-dimethoxypropiophenone(7.6 g, 0.04 mol) and 2′-bromo-3,4-dimethoxypropiophenone (10.52 g, 0.04 mol.) in liquid NH_3 (90 ml) in the presence of Na (1.02 g, 0.044 mol.) was carried out as described by Perry *et al.* (13). Crystallization from MeOH gave the racemic dione **4** (6 g, 78%). The filtrate was concentrated to dryness, the residue dissolved in C_6H_6, and chromatographed on silica gel (150 g). Elution with 2-5% Me_2CO in

C_6H_6, gave an additional amount of **4** (0.5 g) followed by the by-product **17**, which was recovered and crystallized from MeOH; mp 159°; yield, 0.8 g; uv λ max 283 nm; ir, 3520, 1580, 1480, 1230, 1120, 1005 cm^{-1}; ^1H nmr δ 0.63, t, 6H; (2×CH_3); 1.83, m, 4H (2×CH_2); 2.56, s, 2H (2×OH); 3.80, s, 12H (OCH_3); 6.75, s, 6H, (arom. H). *Anal.* calcd. for $C_{20}H_{30}O_6$: C, 67.67; H, 7.74. Found: C, 67.48; H, 7.81.

A solution of **17** (0.1 g) in MeOH (10 ml) was treated with 2N H_2SO_4 (1 ml) and 2N aqueous $NaIO_4$ (2 ml). After 2 h the mixture was shaken with C_6H_6, the solvent layer concentrated to dryness, and the solid crystallized from C_6H_{14}; mp 58°. It was identical with 3,4-dimethoxypropiophenone (13).

4,4'-*Bis*(3,4-DIMETHOXYPHENYL)HEXANE-3-ONE (**18**).—A solution of **17** (0.1 g) in C_6H_6 (10 ml) was stirred with CF_3CO_2H (0.5 ml) for 4 h. It was washed with aqueous $NaHCO_3$ and H_2O, dried (Na_2SO_4), and the C_6H_6 layer concentrated to dryness. Preparative tlc (5% Me_2CO in C_6H_6) gave a chromatographically homogenous glassy solid; yield, 0.08 g; uv λ max, 282 nm; ir 1705 cm^{-1}; ^1H nmr δ 0.65, t, 3H (CH_3); 0.83, t, 3H (CH_3); 2.28, m, 4H (2×CH_2); 3.78, s, 12H (OCH_3); 6.84, m, 6H (arom. H); ms *m/z* 372, 315, 57. *Anal.* calcd. for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58. Found: C, 70.81; H, 7.63.

2,5-*Bis*(3,4-DIMETHOXYPHENYL)- 3,4-DIMETHYL-2-HYDROXY-TETRAHYDROFURAN (**19**).—A mixture of **4** (0.39 g) and $NaBH_4$ in THF (10 ml) and MeOH (10 ml) was stirred at 20° for 30 min. After addition of H_2O (50 ml), extraction with Et_2O and concentration of the solvent layer, the solid was crystallized from MeOH; mp 165°; yield 0.21 g; uv λ max 232, 280 nm; ir 3500 cm^{-1}; ^1H nmr δ 1.01, d, 6H (2×CH_3); 2.0, m, 2H (2×CH); 3.83, s, 12H (OCH_3); 4.64, d, 1H (Ar-CH-o); 7.0, m, 6H (arom. H). *Anal.* calcd. for $C_{22}H_{28}O_6$: C, 68.02; H, 7.27. Found: C, 68.21; H, 7.12.

2,5-*Bis*(3,4-DIMETHOXYPHENYL-3,4-DIMETHYL-Δ^2-DIHYDROFURAN (**20**).—To a solution of **19** (0.1 g) in C_6H_6 was added a 1:10 BF_3 etherate in C_6H_6 (0.1 ml). After 10 min it was washed with H_2O and the C_6H_6 layer concentrated to dryness. The solid was crystallized from Et_2O; mp 89°; yield, 0.07 g; uv λ max 280, 230 nm with a shoulder at 310 nm; ir 1640 cm^{-1}; ^1H nmr δ 1.23, d, 3H (CH_3); 1.90, s, 3H (CH_3); 3.0, m, 1H (*CH*-CH_3); 3.88, s, 12H (OCH_3); 4.90, d, 1H (Ar-CH-O); 7.0, m, 6H (arom. H). *Anal.* calcd. for $C_{22}H_{26}O_5$: C, 71.33; H, 7.08. Found: C, 71.45, H, 7.12.

Alternatively, a mixture of **19** (0.1 g), Ac_2O (2 ml), and pyridine (0.5 ml) was heated at 100° for 30 min. The solid which separated on adding H_2O was filtered and crystallized from Et_2O. It was identical with **20**.

2,5-*Bis*(3,4-DIMETHOXYPHENYL)-3,4-DIMETHYLFURAN (**21**).—A mixture of **19** (0.1 g), 5% Pd/C (0.05 g) in oxydiethanol (5 ml) was boiled under reflux for 2 h. The filtered mixture was diluted with H_2O (20 ml) and extracted with Et_2O. Concentration of the solvent layer gave a crystalline solid; mp 170°, identical with an authentic sample prepared by the method of King and Wilson (14).

VERAGUENSIN (**2**).—Compound **20** (0.2 g) in EtOAc (20 ml) was hydrogenated in the presence of 5% Pd/C (0.05 g) in a Parr apparatus for 2 h. The filtered mixture was concentrated to dryness and the solid crystallized from MeOH; mp 128°; yield, 0.18 g. It was identical with an authentic sample of veraguensin (**2**) (1).

GALBELGIN (**1**).—This was prepared by a number of methods starting from **3**, which was obtained according to the method of Biftu *et al.* (6).

(*a*) A solution of **3** (0.2 g) in C_6H_6 (10 ml) was treated with CF_3CO_2H (0.1 ml) *or* BF_3-etherate (0.1 ml) at 0°. After 1 h it was washed with H_2O, the C_6H_6 layer concentrated to dryness and the solid crystallized from MeOH. The product was identical with galbelgin (**1**) (8), yield 0.16 g.

(*b*) Compound **3** (0.2 g) in EtOAc (20 ml) was heated at reflux with $CuBr_2$ (0.2 g) *or* Dowex-50 (200-400 mesh, H^+ form, 0.2 g) for 1 h. The filtered mixture was washed with H_2O and the solvent layer concentrated to dryness. The solid was crystallized from MeOH and was found to be identical with **1**.

(*c*) A solution of **3** (0.2 g) in $CHCl_3$ (10 ml) and HOAc (0.2 ml) was stirred at 20° in the presence of a sunlamp for 24 h. After washing with aqueous $NaHCO_3$ and H_2O, the $CHCl_3$ layer was concentrated to dryness. The solid after crystallization from MeOH was found to be identical with **1**.

CONVERSION OF **3** TO **1, 2,** AND **22**.—To a solution of **3** (0.3 g) in pyridine (20 ml) was added CH_3SO_2Cl (0.5 ml). After 16 h it was diluted with H_2O, acidified (pH 2) and extracted with Et_2O. The concentrated Et_2O extract was crystallized from MeOH to yield **1** (0.12 g). The filtrate was concentrated and separated into components by preparative tlc (5% Me_2CO in C_6H_6, developed 3 times). Band 1 was found to be compound **2**, yield, 0.07 g. Band 2 yielded more of compound **1**, (0.02 g). Band 3 was crystallized from MeOH and shown to be identical with **22** (1); mp 80°; yield, 0.025 g.

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