Acknowledgment.—The award of a research grant (AM 13708) from the National Institute of Arthritis and Metabolic Diseases, U. S. Public Health Service (to R. S.), is gratefully acknowledged. We also wish to thank Professor B. Weinstein (University of Washington) for a reference sample of taiwanin C.

Notes

Lignan Lactones. Synthesis of (≡)-Collinusin and Justicidin B[1]

ELLIOTT BLOCK AND ROBERT STEVENSON*

Department of Chemistry, Brandeis University, Waltham, Massachusetts 02154

Received June 4, 1971

There has been considerable activity recently concerning the isolation, structure elucidation, and synthesis of lignan lactones. At least 14 members[2-18] of this group of natural products have known constitutions based on 2, 3-dimethylnaphthalene. In addition, three further natural products,[19-22] which are based on a phenyldihydronaphthalene parent, have recently been described. We report here a synthesis of (≡)-collinusin (I) and justicidin B (II), a representative of each class.

Cleistanthus collinus (Roxb.) Benth. & Hook is a highly poisonous plant which has reputedly been used for insecticidal, piscicidal, and suicidal purposes.[23] From the leaves, Govindachari and coworkers isolated ellagic acid, diphyllin, and two new lactones which were named cleistanthin (a glycoside of diphyllin) and collinusin for which the structure I was proposed.[19,24] The synthesis of this lactone which we have undertaken is in complete support of this structure. The route we have utilized is based on the procedure developed by Klemm and his coworkers for a general synthesis of lignan lactones and demonstrated specifically for γ-apopicropodophyllin and dehydro-β-peltatin methyl ether.[25-27] It appeared that this pathway would be readily adaptable to collinusin; the key step (V → I), however, involving the cyclization of a cinnamyl phenylpropiolate ester to a phenyl dihydronaphthalene lactone was not entirely satisfactory, and the derived product I could only be separated from the reaction mixture with considerable difficulty and loss. The lack of specificity in cyclization may limit the general applicability of this pathway.

The key intermediate was 3, 4-dimethoxycinnamyl 3, 4-methylenedioxyphenylpropiolate (V), conveniently obtained by heating 3,4-methylenedioxyphenylpropiolic acid chloride (III) with 3,4-dimethoxycinnamyl alcohol (IV, R = H). Since the crude ester had infrared and nuclear magnetic resonance spectra in complete accord with structure V, it was used without further purification and heated under reflux with acetic anhydride to effect cyclization. Thin layer chromatographic examination of the product indicated the presence of three principal constituents, of which the fastest running, readily separable from the other two, was identified by comparison with an authentic specimen as 3,4-dimethoxycinnamyl acetate (IV, R = CH_3CO).

Satisfactory separation of the two other components was only achieved by a repetition of the thin layer chromatographic separation and recrystallization. The slower running compound (obtained pure in 9% yield) had constants in accord with the proposed structure, 3,4-dihydro-6,7-dimethoxy-3-hydroxymethyl-1-(3′,4′-methylenedioxyphenyl)naphthalene-2-carboxylic acid lactone (I). A direct comparison of the nmr spectra of this synthetic product and natural collinusin confirmed the structure.[28]

(1) (a) The awards of a research grant (AM 13708) from the National Institute of Arthritis and Metabolic Diseases, and Institutional Grant (IN-29) from the American Cancer Society and a Fellowship (to E. B.) from the Gillette Co., are gratefully acknowledged. (b) A preliminary communication outlining this work has appeared: E. Block and R. Stevenson, *Chem. Ind. (London)*, 894 (1970).

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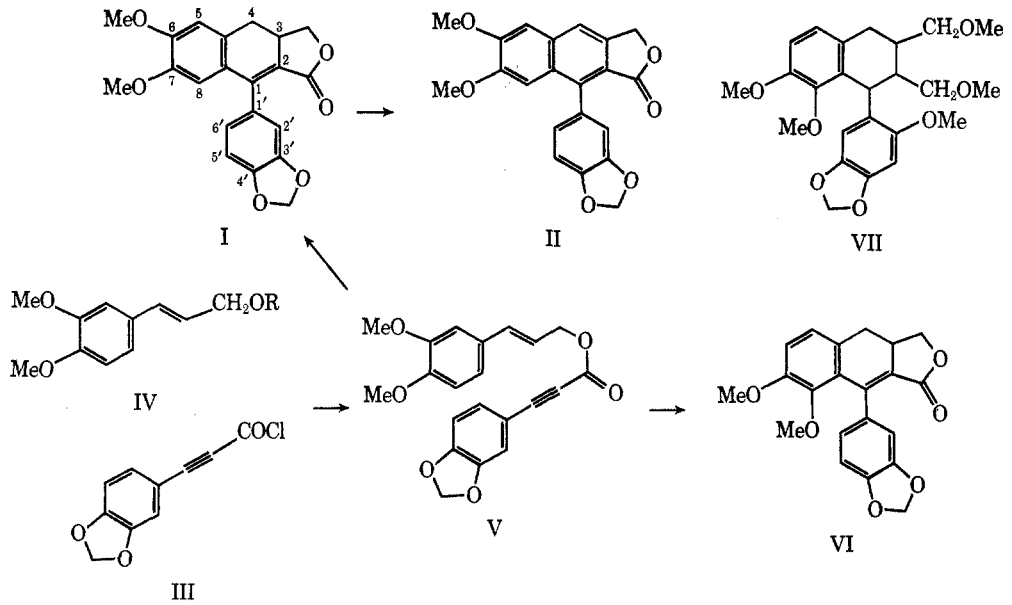

The third product (obtained pure in 5% yield) was isomeric with collinusin and is formulated as 3,4-dihydro-7,8-dimethoxy-3-hydroxymethyl-1-(3′,4′-methylenedioxyphenyl)naphthalene-2-carboxylic acid lactone (VI), *i.e.*, the product formed by cyclization ortho to the original 3-methoxyl group rather than para as in the formation of collinusin. Of diagnostic significance in the nmr spectrum, the upfield singlet signal at δ 6.57 of collinusin, attributable to the aromatic H-8 proton being shielded by ring C, is absent and replaced by the signal (δ 3.22) attributable to a shielded methoxyl group attached to C-8. Previous study of the generality of cyclization of substituted *trans*-cinnamylphenylpropiolates[26] indicated that there could be obtained, in addition to the lactone of type I (*i.e.*, 6,7-disubstituted), a product which was probably a molecular compound composed of lactone types I and VI (*i.e.*, 7,8 disubstituted); since, however, efforts to separate the components were unsuccessful, this postulate was deemed tentative and an alternative explanation suggested. In view of the fact that we have now separated (with considerable difficulty) and identified the two pure lactones I and VI, the composite nature of these earlier products is supported. With the establishment of the location of the methoxyl groups at C-7 and C-8 in product VI, it is of interest that the recently revised[29] structure VII for the phenyltetralin lignan, hypophyllanthin, incorporates this same structural feature.

Govindachari and coworkers[19,24] obtained dehydrocollinusin (II) by palladium–carbon dehydrogenation of (+)-collinusin and noted that the physical constants were strikingly close to those reported for justicidin B, a piscicidal extractive isolated by Munakata and coworkers[6,7] from *Justicia Hayatai* var. *decumbens*, although the unavailability of justicidin B precluded a direct comparison. We have now shown that (≡)-collinusin is very smoothly oxidized to dehydrocollinusin by the action of *N*-bromosuccinimide. Comparison of the nmr spectrum[28] of our synthetic dehydrocollinusin with that obtained from natural collinusin and now with justicidin B[30,31] establishes the identity. A six-stage synthesis of justicidin B from methyl eugenol oxide in an overall yield of 1–2% has been communicated.[7]

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Experimental Section

Melting points are uncorrected. Infrared spectra (ν) were recorded using a Perkin-Elmer Model 137 spectrophotometer and ultraviolet spectra (λ, nm) with a Cary 14 spectrophotometer. Nuclear magnetic resonance spectra (δ, ppm) were determined for solutions in deuteriochloroform with tetramethylsilane as internal reference at 60 MHz; J values are in hertz.

3,4-Dimethoxycinnamyl Alcohol (IV, R = H).—A solution of methyl 3,4-dimethoxycinnamate[32] (11.1 g) in ether (250 ml) was added to lithium aluminium hydride (3.93 g) in the same solvent (300 ml) at −10 to −15° over 3 hr. Stirring was continued for a further hour and the product worked up in the usual way. Evaporation of the ether extract gave the alcohol as a slightly yellow solid, mp 64–72° (lit.[33] mp 78°), used without further purification; ν (KBr) 3571 cm^{-1} (hydroxyl); δ 2.12 br (OH group), 3.85 s (two OCH_3 groups), 4.28 d (J = 5 Hz, allylic hydroxymethylene group), 5.96–6.72 m (two vinyl protons), and 6.75–7.03 m (three Ar H).

3,4-Methylenedioxyphenylpropiolic Acid Chloride (III).—3,4-Methylenedioxyphenylpropiolic acid[34] (774 mg) was added to an excess of freshly purified thionyl chloride, the mixture stirred at room temperature until solution was complete, and the excess thionyl chloride removed by repeated addition of benzene and evaporation under reduced pressure. The residual acyl chloride had ν ($CHCl_3$) 2203 (C≡C), 1761 and 1736 cm^{-1} (COCl); δ 6.05 s (methylenedioxy group), 6.85 d (J = 8.5 Hz, H-5), 7.03 d (J = 1.3 Hz, H-2), 7.25 q (J = 1.3, 8.5 Hz, H-6).

3,4-Dimethoxycinnamyl 3,4-Methylenedioxyphenylpropiolate (V).—A mixture of acid chloride III (830 mg), 3,4-dimethoxycinnamyl alcohol (801 mg), and pyridine (0.4 ml) in benzene (15 ml) was heated under reflux for 5 hr, cooled, and then washed successively with water, 2 *N* hydrochloric acid, water, saturated sodium carbonate solution, and water. Evaporation of the dried (Na_2SO_4) extract gave the crude ester as an oil (1.57 g): ν ($CHCl_3$) 2225 (C≡C), 1712 (ester), and 965 cm^{-1} (trans alkene); δ 3.83 s and 3.85 s (OCH_3 groups), 5.95 s (methylenedioxy group), 4.84 d (J = 6 Hz, methylene group), and 6.0–7.3 m (aromatic and vinyl protons).

Cyclization of 3,4-Dimethoxycinnamyl 3,4-Methylenedioxy-

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phenylpropiolate.—The crude ester (1.35 g) was dissolved in acetic anhydride (25 ml) and heated under reflux for 11 hr, the solvent removed under reduced pressure, and the residue subjected to thin layer chromatography on silica gel PF (1.0 mm) using ethyl acetate–chloroform (1:9). Two principal zones (R_f 0.46 and 0.53) which overlapped were separated and eluted, and the chromatographic treatment was repeated.

Crystallization of the slower running component from acetone–petroleum ether (bp 60–110°) and then propanol yielded **3,4-dihydro-6,7-dimethoxy-3-hydroxymethyl-1-(3′,4′-methylenedioxyphenyl)naphthalene-2-carboxylic acid lactone** [(±)-**collinusin**] (I) as a white solid (121 mg): mp 195–198°; ν (KBr) 1742 (conj γ-lactone), 1626, 1603, 1565, 1502 and 928 cm^{-1}; λ (C_2H_5OH) 248 nm (log ϵ 4.18) and 344 (3.99); δ 3.66 s (C-7 methoxyl), 3.90 s (C-6 methoxyl), 5.98 s (methylenedioxy group), 6.57 s (H-8), 6.80 br (four Ar H), and 2.67–4.82 complex m (5 protons; benzylic, allylic, and lactone methylene protons).

Anal. Calcd for $C_{21}H_{18}O_6$: C, 68.84; H, 4.95. Found: C, 68.36; H, 5.17.

Crystallization of the faster running component from methylene chloride–petroleum ether (bp 38–54°) yielded **3,4-dihydro-7,8-dimethoxy-3-hydroxymethyl-1-(3′,4′-methylenedioxyphenyl)-naphthalene-2-carboxylic acid lactone** (VI) as a white solid (63 mg): mp 213–215°; ν 1748 (conj γ-lactone), 1631, 1542, 1484, and 937 cm^{-1}; λ (C_2H_5OH) 240 nm (log ϵ 4.13) and 295 (4.15); δ 3.22 s (C-8 methoxyl), 3.80 s (C-7 methoxyl), 5.96 s (methylenedioxy group), 6.80–6.95 (five Ar H), and 2.62–5.40 complex m (5 protons, benzylic, allylic, and lactone methylene protons).

Anal. Calcd for $C_{21}H_{18}O_6$: C, 68.84; H, 4.95. Found: C, 69.04; H, 5.00.

Elution of a still faster running zone (R_f 0.62) yielded an oil (48 mg) identified as **3,4-dimethoxycinnamyl acetate** (IV, R = $COCH_3$)[35] by comparison with an authentic sample prepared by treatment of 3,4-dimethoxycinnamyl alcohol with acetic anhydride in pyridine. It had ν 1730 (carbonyl) and 966 cm^{-1} (trans alkene); δ 2.08 s (acetate methyl group), 3.87 s and 3.88 s (methoxyl groups), 4.72 d (J = 6 Hz, allylic CH_2), 5.90–6.72 m (two vinyl protons), and 6.77–7.12 m (three Ar H).

Conversion of (±)-Collinusin to Justicidin B.—A mixture of collinusin (25.5 mg), *N*-bromosuccinimide (15 mg), and benzoyl peroxide (2 mg) in carbon tetrachloride (20 ml) was heated under reflux for 10 min during which time the solution turned yellow and then for a further 20 min after which time the color had been discharged. The cooled and filtered solution was evaporated under reduced pressure and the residue chromatographed on a silica gel PF plate (1.0 mm) with ethyl acetate–chloroform (1:9). Elution of the zone R_f 0.31 yielded a product (24 mg) which on crystallization from acetone–ether gave **6,7-dimethoxy-3-hydroxymethyl-1-(3′,4′-methylenedioxyphenyl)naphthalene-2-carboxylic acid lactone** (**justicidin** B) (II) as needles: mp 237–238° (lit.[31] mp 240°); ν (KBr) 1761 (lactone), 1623 and 933 cm^{-1}; λ ($CHCl_3$) 260 nm (log ϵ 4.77), 296 (4.02), 308 (4.02), and 350 (3.73); δ 3.80 s (C-7 methoxyl), 4.03 s (C-6 methoxyl), 5.37 d (J = 1 Hz, lactone methylene), 6.00 d and 6.07 d (J = 1.5 Hz, methylenedioxy group), and 6.75–7.70 (five Ar H).

Registry No.—I, 28982-10-7; II, 17951-19-8; III, 31337-55-0; IV (R = H), 18523-76-7; IV (R = $COCH_3$), 31337-58-3; V, 28908-38-5; VI, 31337-60-7.

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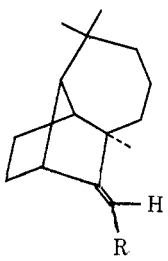
Base-Catalyzed Rearrangement of ω-Bromolongifolene

GOVERDHAN MEHTA

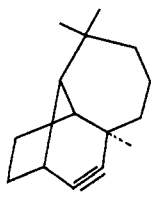
Department of Chemistry, Indian Institute of Technology, Kanpur-16, India

Received March 16, 1971

We wish to report here the generation and capture of a highly strained tricycloalkyne,[1] the 3,8,8-trimethyltricyclo[7.3.0.0^{4,10}]dodec-2-yne (**3**) (longifolyne), *via* a base-induced Fritsch–Buttenberg–Wiechell rearrangement[2] of ω-bromolongifolene (**2**). Bhattacharyya and coworkers[3] have recently reported that fusion of **2** with potassium hydroxide at 400° gave a mixture of ring-expanded ketones, longihomocamphenilone (**4**) and longiisohomocamphenilone (**5**), in 5–7% yield together with a dimeric dilongifolenyl ether (**6**). The nature of the ring enlargement products was suggestive of the possible intermediacy of cycloalkyne **3** in the alkali fusion reaction. The intervention of **3** in the rearrangement of ω-bromolongifolene with potassium *tert*-butoxide is described here.



1, R = H
2, R = Br



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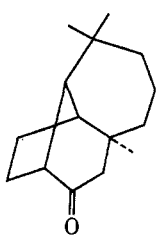

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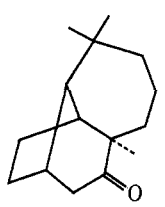

5

Longifolene (**1**) was converted into ω-bromolongifolene (**2**) in one step *via* vinylic bromination with *N*-bromosuccinimide in refluxing benzene. The diagonistic feature of the nmr spectrum was the appearance of the olefinic proton singlet at τ 4.37 and an allylic bridgehead proton signal at τ 6.87 [*cf.* longifolene (**1**) at τ 7.42]. The strong deshielding[4] of the allylic bridgehead proton leads to assignment of bromine as anti with respect to the large ring. This is in conformity with the X-ray crystal structure[5] of **2**. On refluxing with potassium *tert*-butoxide in toluene the ω-bromomethylene derivative **2** readily rearranged to cycloalkyne **3** and was trapped with 1,3-diphenylisobenzofuran to furnish an adduct, mp 254–256°, in 85% yield. The adduct is devoid of any olefinic proton absorption in the nmr spectrum but exhibits signals at τ 9.11, 9.30, and 9.51 (3 H, s, Me), 7.25 (1 H, broad, allylic bridgehead), and 1.8–1.3 (14 H, m, aromatic) leading to its formulation as **7**. The endo geometry of the ether bridge in **7** is deduced from the steric considerations as well as exceptional shielding (τ 9.51) of the C_8-methyl group due to the diamagnetic anisotropy of the phenyl ring. The acetylene **3** could also be trapped with tetracyclone **8** to

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(5) Private communication from Professor G. Ourisson. We wish to thank Professor Ourisson for this information and a sample of ω-bromolongifolene.