Synthesis of Two Benzofuran Neolignans

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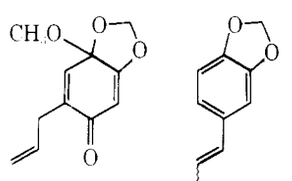
Condensation of 2-allyl-3,4,4-trimethoxycyclohexa-2,5-dienone (**15**) with (*E*)-isosafrole (**2**) in acetonitrile–methanol under the influence of trinitrobenzenesulfonic acid yielded a mixture of the dihydrobenzofuran **10** and the bicyclooctane **18**. Bicyclooctane **18** was unstable toward acids and isomerized rapidly to the dihydrobenzofuran **9**, the racemate of an *Aniba terminalis* constituent. Dehydrogenation with DDQ gave benzofuran **11**, another naturally occurring neolignan.

In a recent paper from this laboratory[1] the total syntheses of the neolignans guianin (**3**)[2] and burchellin (**4**),[3] from



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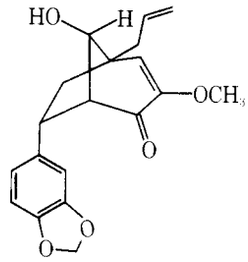

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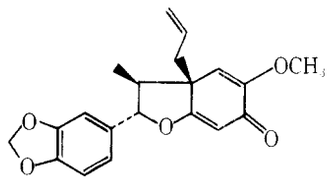

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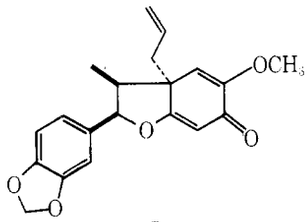

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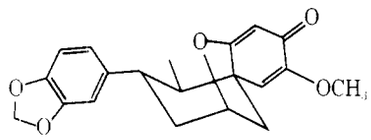

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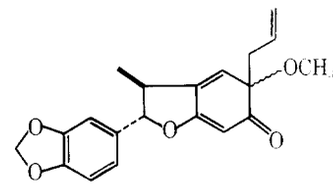
products formed in the acid-catalyzed condensation of the *p*-quinone ketal **1** with (*E*)-isosafrole (**2**), were described. Similarly, 2-*epi*-3a-*epi*-burchellin (**5**)[4] and futoenone (**6**)[5] were prepared starting from the same ketal **1** and (*Z*)-isosafrole (**2**). To account for the products formed in these acid-induced condensations it was postulated that bicyclo[3.2.1]-octanes with endo oriented aryl groups were the initial products resulting from concerted [2 + 4] cycloadditions. Subsequent isomerization of the kinetic adducts could have led to the more stable hydrobenzofurans with configurations corresponding to those present in the natural products **4** and **5**. Alternatively, the bicyclooctanes could have isomerized to spiro[5.5]undecanes, and the intermediate derived from (*Z*)-isosafrole (**2**) was assumed to have undergone a further cyclization to a product with a futoenone skeleton.

Certain *Aniba* species[4,6] produce the neolignans **7**, **8**, **9**, and **11**, in addition to metabolites of the guianin (**3**) and burchellin (**4** and **5**) types. The possibility that **7**, **8**, and **9** originate in vivo from the same eugenol-isoeugenol dimer by sequential Cope, retro-Claisen, and Claisen rearrangements is not unreasonable but awaits verification. It occurred to us that the dihydrobenzofuran **9** could also arise from a hitherto unknown bicyclooctane **18**, which in turn could be the outcome of a cycloaddition of *p*-quinone ketal **15** to (*E*)-isosafrole (**2**). The intermediate bicyclooctane **18** was anticipated to rearrange irreversibly to the *Aniba* constituent **9**. We have reduced this



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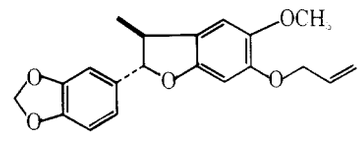

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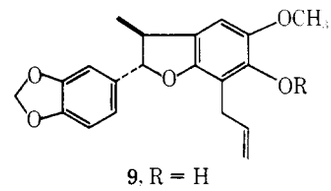
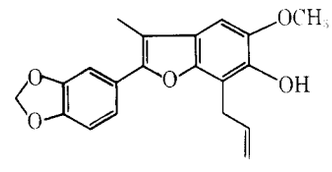


9, R = H
10, R = CH_3



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scheme to practice, and in this paper we report the synthesis of the two neolignans **9** and **11**.

The tetrahydropyranyl ether **12** on metalation with *n*-butyllithium afforded the C_2 lithio dervative **13**. Alkylation of the corresponding cuprate with allyl bromide followed by hydrolytic removal of the protecting group furnished phenol **14**.[7] Oxidation to the *p*-benzoquinone ketal **15** was accomplished with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in methanol solution.[8] Ketal **15** was found to condense with (*E*)-isosafrole (**2**) in acetonitrile containing methanol and added 2,4,6-trinitrobenzenesulfonic acid to give an easily separable mixture of adducts consisting of the dihydrobenzofuran **10** (42% yield) and the bicyclooctane **18** (20% yield). In agreement with expectation, trifluoromethanesulfonic acid mediated isomerization of **18** gave the crystalline phenol **9**. Comparison of its ^1H nuclear magnetic resonance spectrum with that of an oily mixture of both cis and trans isomers isolated from *Aniba terminalis*[4] left no doubt that the synthesis produced the more stable trans isomer. Incidentally, this synthesis proves the relative positions of the hydroxy and methoxy groups and thus confirms the earlier conclusion based on nuclear magnetic resonance arguments.[4] The formation of the two adducts is accommodated by a scheme in

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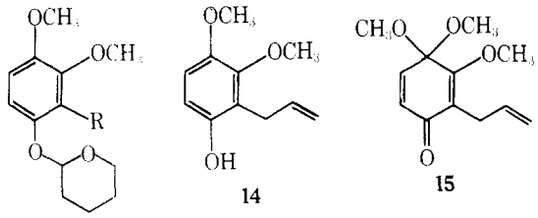
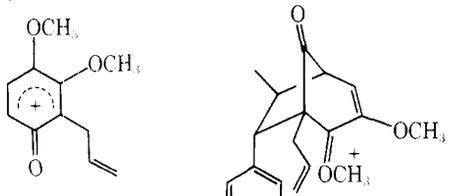


12, R = H
13, R = Li



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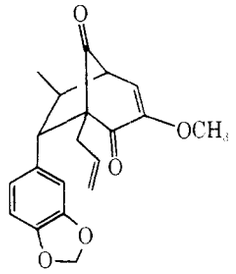
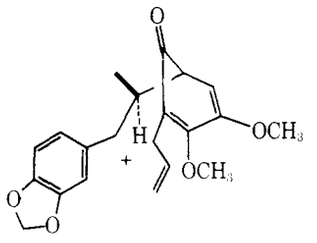


18



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which cation **16** and olefin **2** align themselves in a manner that favors bond formation between the most electrophilic C_6 atom of the cation **16** and the terminal carbon atom of the electron-rich olefin. A concerted [2 + 4] cycloaddition would create the oxonium ion **17**, with an endo oriented aryl group, that is captured by methanol. Hydrolysis of the hypothetical ketal during workup would give the observed bicyclooctane **18**. Alternatively, oxonium ion **17** once formed could isomerize to the benzylic cation **19**, which in turn could cyclize to the dihydrobenzofuran **10**. Ion **19** could also be the result of a process in which only one carbon–carbon bond was formed in the first step, but the stereoselective formation of a single bicyclooctane is in better agreement with a concerted rather than a stepwise process.

Finally, dehydrogenation of the dihydrobenzofuran **9** with DDQ afforded the benzofuran **11**, identical according to melting point and NMR spectrum with the natural material.[4]

Experimental Section

Melting points were determined on a Reichert hot stage microscope and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer 237B or 247 grating spectrophotometer and are reported in wavenumbers (cm^{-1}). Nuclear magnetic resonance (NMR) spectra were measured on a Varian T-60 or a Perkin-Elmer R-22 spectrometer and are given in parts per million (δ) downfield from tetramethylsilane as an internal standard; the abbreviations s, d, and m refer to singlet, doublet, and multiplet, respectively. Ultraviolet (UV) spectra were determined on a Perkin-Elmer 200 spectrophotometer, and wavelengths are reported in nanometers (nm). High-resolution mass spectra (HRMS) were measured on a DuPont CEC-110B instrument, and low-resolution mass spectra (MS) were determined on a Varian Mat 44 instrument. Elemental analyses were performed by Robertson Laboratory, Florham Park, N.J.

3,4-Dimethoxyphenol Tetrahydropyranyl Ether (12). The tetrahydropyranyl ether of 3,4-dimethoxyphenol was prepared in a standard fashion using *p*-toluenesulfonic acid monohydrate as catalyst in dichloromethane at room temperature for 2 h. Bulb-to-bulb distillation in a Büchi GKR-50 Kugelrohrapparat gave **12** as a colorless oil in 97% yield: bp 160 °C (0.02 mm); IR (CCl_4) 2943, 1511, 1230, 1155, 1122, 1100, 1031, 1017 cm^{-1}; NMR (CCl_4) δ 1.30–2.13 (m, 6), 3.73 (s, 3), 3.77 (s, 3), 3.30–4.10 (m, 2), 5.15–5.32 (m, 1), 6.17–6.77 (m, 3). Anal. Calcd for $C_{13}H_{18}O_4$: 238.12051. Found: 238.12347.

2-Allyl-3,4-dimethoxyphenol (14). To a cooled (ice bath) and stirred solution of tetrahydropyranyl ether **12** (8.32 g, 35 mmol) in anhydrous THF (80 mL) under nitrogen was added dropwise via a syringe 21 mL of *n*-BuLi (2.45 M in hexane; 52 mmol). The ice bath was removed after the addition was completed, and the resulting solution was stirred for 30 min and then left at room temperature overnight. Copper iodide (6.70 g, 35 mmol) was added in small portions to the stirred solution which was continually stirred for 1 h at room temperature. The solution was cooled (ice bath) and allyl bromide (4.5 mL, 6.3 g, 52 mmol) added via a syringe. The ice bath was removed after addition was completed, and the solution was stirred at room temperature for 1 h and then heated to reflux for 2 h. The solution was cooled and water (80 mL) added. The contents were then filtered through a pad of Celite, and ether (1 × 300 mL and 1 × 200 mL) was used to extract the filtrate. The combined ether extracts were washed with saturated aqueous ammonium chloride (1 × 100 mL) and then brine (1 × 100 mL), and the ethereal solution was concentrated in vacuo. The residue was dissolved in 135 mL of 90% aqueous methanol and 13.5 mL of 5% oxalic acid. The solution was stirred at room temperature for 1 h, followed by partitioning between water (100 mL) and ether (300 mL). The aqueous phase was separated and extracted further with ether (2 × 200 mL). The combined ether extracts were washed with water (2 × 100 mL), dried ($MgSO_4$), decolorized with charcoal, filtered, and concentrated in vacuo. The residue was then purified by column chromatography on silica gel eluting with hexane–EtOAc (4:1). Fractions judged to be identical by TLC were pooled and gave 4.18 g of **14** as a yellow oil (62% yield): IR (CCl_4) 3450, 1500, 1633, 1267, 1054, 992, 908 cm^{-1}; NMR (CCl_4) δ 3.42 (br d, 2, J = 6 Hz), 3.77 (s, 3), 3.80 (s, 3), 4.80–5.27 (m, 2), 5.68–6.30 (m, 1), 6.17 (br s, 1), 6.43 (d, 1, J = 9 Hz), 6.65 (d, 1, J = 9 Hz).

2-Allyl-3,4,4-trimethoxycyclohexa-2,5-dienone (15). To a stirred solution of DDQ (0.267 g, 1.2 mmol) in a minimum amount of methanol at room temperature was added dropwise a solution of **14** (0.190 g, 1.0 mmol) in methanol (98 mL). After addition was completed, methanol was removed in vacuo and the residue was dissolved in ether. The ethereal solution was then washed with saturated $NaHCO_3$ solution and water, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was chromatographed on a 20 × 20 × 0.1 cm silica gel plate using hexane–EtOAc (4:1 v/v) as solvent to give 0.165 g of **15** as a yellow oil (75% yield; about 92% pure by NMR): IR (CCl_4) 1675, 1639, 1612 cm^{-1}; NMR (CCl_4) δ 3.03 (br d, 2, J = 6 Hz), 3.35 (s, 6), 4.15 (s, 3), 4.75–5.22 (m, 2), 5.45–6.07 (m, 1), 6.25 (d, 1, J = 10 Hz), 6.47 (d, 1, J = 10 Hz); UV (95% EtOH) 227 nm (sh, ϵ 9100), 315 (3900). Anal. Calcd for $C_{12}H_{16}O_4$: 224.10486. Found: 224.10649.

***trans*-2,3-Dihydro-7-allyl-5,6-dimethoxy-3-methyl-2-(3,4-methylenedioxyphenyl)benzofuran (10) and 1-Allyl-3-methoxy-6-*exo*-methyl-7-*endo*-(3,4-methylenedioxyphenyl)bicyclo[3.2.1]oct-3-ene-2,8-dione (18).** A solution of **15** (68 mg, 0.3 mmol; about 92% pure) and isosafrole (90 μL, 101 mg, 0.6 mmol) in anhydrous acetonitrile (3 mL) containing 25 μL of methanol (18 mg, 0.6 mmol) was cooled in a dry ice–3-pentanone bath under nitrogen. A catalytic amount of trinitrobenzenesulfonic acid was then added, and the solution was stirred for 30 min. The cooling bath was removed and saturated $NaHCO_3$ solution added. The contents were transferred to a separatory funnel and extracted twice with ether. The combined ether extracts were washed with water twice, dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed on a 20 × 20 × 0.1 cm silica gel plate using hexane–EtOAc (3:1 v/v) as solvent to give 38 mg of **10** (42%) and 17 mg of **18** (20%).

Dihydrobenzofuran 10: mp 67–69 °C (hexane); IR (CCl_4) 1468, 1251, 1043 cm^{-1}; NMR (CCl_4) δ 1.37 (d, 3, J = 7 Hz), 3.33 (br d, 2, J = 6 Hz), 3.08–3.47 (m, 1), 3.78 (s, 6), 4.87–5.20 (m, 2), 4.97 (d, 1, J = 9 Hz), 5.96 (s, 2), 5.76–6.20 (m, 1), 6.52 (br s, 1), 6.74–6.93 (m, 3); MS *m/e* (relative intensity, %) 354 (M^+, 100). Anal. ($C_{21}H_{22}O_5$) C, H.

Bicyclooctane 18: mp 117–119 °C (methanol); IR (CCl_4) 1766, 1695, 1612 cm^{-1}; NMR ($CDCl_3$) δ 1.14 (d, 3, J = 7 Hz), 2.18–2.69 (m, 3), 2.80–3.07 (m, 2), 3.66 (s, 3), 5.04–5.36 (m, 2), 5.86 (s, 2), 5.56–6.13 (m, 1), 6.29–6.73 (m, 4); MS *m/e* (relative intensity, %) 340 (M^+, 5), 178 (69), 162 (100). Anal. ($C_{20}H_{20}O_5$) C, H.

***trans*-2,3-Dihydro-7-allyl-6-hydroxy-5-methoxy-3-methyl-2-(3,4-methylenedioxyphenyl)benzofuran (9).** A solution of **18** (32.5 mg) in dry acetonitrile (1 mL) was cooled in an ice bath. One drop of trifluoromethanesulfonic acid was added, and the solution was stirred for 30 min. Saturated $NaHCO_3$ solution was added, and the contents were extracted with ether. The ether solution was dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed on a 20 × 20 × 0.05 cm silica gel plate using hexane–EtOAc (4:1 v/v) as solvent to give 17.3 mg (53%) of **9**: mp 79–80 °C (hexane);

IR ($CHCl_3$) 3546, 1466, 1334, 1243, 1031 cm^{-1}; NMR ($CDCl_3$) δ 1.36 (d, 3, J = 7 Hz), 3.40 (br d, 2, J = 6 Hz), 2.90–3.53 (m, 1), 3.85 (s, 3), 4.83–5.30 (m, 2), 5.01 (d, 1, J = 9 Hz), 5.68 (s, 1), 5.95 (s, 2), 5.47–6.40 (m, 1), 6.53 (br s, 1), 6.72–7.00 (m, 3); MS m/e (relative intensity, %) 340 (M^+, 100).

7-Allyl-6-hydroxy-5-methoxy-3-methyl-2-(3,4-methylenedioxyphenyl)benzofuran (11). Starting with 107 mg (0.3 mmol) of **18**, 98 mg of crude dihydrobenzofuran **9** was obtained using the conditions described above. The crude dihydrobenzofuran **9** was then dissolved in THF (1 mL) and cooled in an ice bath while a solution of DDQ (65 mg, 0.3 mmol) in THF (1 mL) was added dropwise to it. After 10 min, the contents were diluted with ether and then washed with water. The aqueous washing was back extracted with ether, and the combined ether extracts were washed with saturated NaCl solution, dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed on a 20 × 20 × 0.1 cm silica gel plate using hexane–EtOAc (6:1 v/v) as solvent to give 45 mg (42%) of **11**: mp 123–124 °C (hexane–diethyl ether); IR ($CHCl_3$) 3567, 1475, 1350, 1258, 1046 cm^{-1}; NMR ($CDCl_3$) δ 2.38 (s, 3), 3.72 (br d, 2, J = 7 Hz), 3.94 (s, 3), 4.98–5.33 (m, 2), 5.83 (s, 1), 6.01 (s, 2), 5.89–6.40 (m, 1), 6.80 (s, 1), 6.91 (d, 1, J = 8 Hz), 7.18–7.36 (m, 2); UV (95% EtOH) 254 nm(log ϵ 3.92), 290(sh, 4.16), 328 (4.51);[9] MS m/e (relative intensity, %) 338 (M^+, 100).

Acknowledgment. We are indebted to the National Institutes of Health (GM 09686) and the Hoffmann-La Roche Foundation for financial support. High-resolution mass spectra were measured in the National Institutes of Health supported facility at the Massachusetts Institute of Technology (Grant FR 00317) under the direction of Professor K. Biemann.

Registry No.—**2,** 4043-71-4; **9,** 67010-45-1; **10,** 66967-24-6; **11,** 57467-91-1; **12,** 66967-25-7; **14,** 66967-26-8; **15,** 66967-27-9; **18,** 66967-28-0; allyl bromide, 106-95-6.

References and Notes

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(8) G. Büchi, P.-S. Chu, A. Hoppmann, C.-P. Mak, and A. Pearce, *J. Org. Chem.*, submitted for publication.
(9) The values given in ref 4 are 250, 290, and 337 nm (log ϵ 3.83, 4.06, and 4.44).

A Useful Synthesis of 3-Oxodihydroisoindoles

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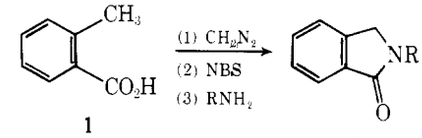
Received April 20, 1978

A useful one-step conversion of *o*-acylbenzoic acids (**3**) to 3-oxodihydroisoindoles (**4**) has been developed. Thus, reductive amination of **3** with a primary amine, the amine hydrochloride, and sodium cyanoborohydride or sodium borohydride in acetonitrile effected the conversion of **3** to **4**. The success of this method is dependent on the initial formation in acetonitrile of a 1-alkyl-1-(alkylamino)dihydroisobenzofuran-3-one, a "ring tautomer" such as **7**, which on protonation is reduced rapidly to **4** by these metal hydrides. Other nucleophiles (CH_3NH_2 and CN^-) were substituted for the metal hydrides to synthesize 1-substituted analogues of **4** such as 1,2-dimethyl-1-cyano-3-oxodihydroisoindole (**6**).

In the preparation of isoindoles[1] as well as the elaboration of certain natural products,[2,3] 3-oxodihydroisoindoles have served as important synthetic intermediates. Routes of limited utility to these lactams have been described.[4,5] In addition, Danishefsky has reported a useful two-step method to convert methyl *o*-toluate to *N*-methyl-3-oxodihydroisoindole (eq 1).[2] What we believe to be an equally attractive route to 3-oxodihydroisoindoles in general and a better route from *o*-acylbenzoic acids to 1,2-disubstituted analogues specifically is set forth below (eq 2).



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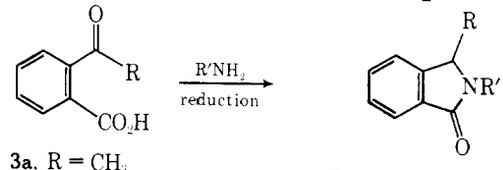

(2)

3a, R = CH_3
b, R = C_2H_5
c, R = n-C_3H_7
d, R = H
e, R = C_6H_5

4a, R = R′ = CH_3
b, R = CH_3; R′ = C_2H_5
c, R = CH_3; R′ = n-C_3H_7
d, R = CH_3; R′ = 
e, R = CH_3; R′ = $C_6H_5CH_2$
f, R = C_2H_5; R′ = CH_3
g, R = n-C_3H_7; R′ = CH_3
h, R = H; R′ = CH_3
i, R = CH_3; R′ = $CH(CH_3)_2$

These lactams (**4**) were required as intermediates for the synthesis of 1,2,3-trisubstituted isoindoles, a class of compounds which has received very limited attention in the literature.[6] Initially, commercially available *o*-acetylbenzoic acid (**3a**) was hydrogenated to *o*-ethylbenzoic acid, and this acid was carried through the three-step process of eq 1 with methylamine as the base to provide **4a.** Although this approach was successful with several other primary amines, it was apparent that an alternate direct route (eq 2) from *o*-acylbenzoic acids **3** to the desired lactams **4** offered certain advantages. Thus, the acids **3** are more readily available either commercially[7] or by synthesis[8] than the corresponding *o*-alkylbenzoic acids which, in fact, frequently are prepared from **3.** Furthermore, this synthesis in comparison with that of eq 1 involved fewer operational steps and avoided the handling of the intermediate bromo esters which are potent lachrymators.

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