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ANODIC OXIDATION OF 2,6-DIMETHOXY-4-ALLYLPHENOL: SYNTHESIS OF ASATONE

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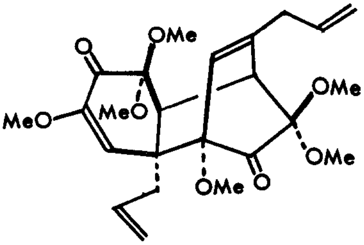
Two novel neolignans, asatone (1) and isoasatone (2), have been isolated from the plant _Asarum teitonense_ Hayata.[1] Furthermore, the former has been photochemically converted into 2.[1] In connection with our synthetic study on asatone, the anodic oxidation of 2,6-dimethoxy-4-allylphenol (3) was carried out under various conditions, affording asatone (1) in a low yield. The present study demonstrates the first example about the phenolic compound having an allyl group as a substituent, although extensive studies have been made on the anodic oxidation of many phenolic compounds.[2]



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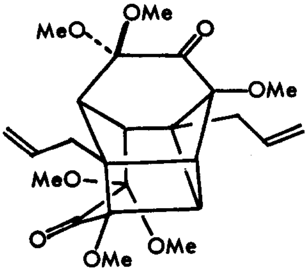

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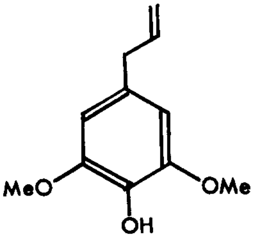


3

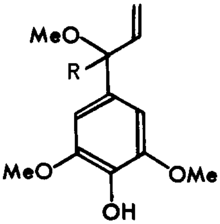
A two-compartment cell with platinum electrodes was used. A methanolic solution of 2,6-dimethoxy-4-allylphenol (3) (200 mg) containing 1N MeONa (10 ml) and LiClO$_4$ (1.6 g) as a supporting salt was electrolyzed at room temperature for _ca._ 30 min at a controlled anodic potential of 400 mV _vs_ SCE. The electrolysis current was gradually decreased from 100 mA to 20 mA. The reaction solution was then concentrated under reduced pressure below 40°, and separated by column chromatography [Polymer HP-255, MeOH-H$_2$O (95 : 5)] followed by preparative TLC [Kieselgel PF$_{254}$, hexane-EtOAc (2 : 3)] to give three oxidation products (4, 5, and 6) in 30, 2.3, and 21% yields, respectively. The compound (5) must be produced from 4 in this reaction, which has been monitored by HPLC:[3] although 4 was a main product at 2.56 Faraday/mole, the peak corresponding to 4 was not detected at 3.92 Faraday/mole but instead the strong peak corresponding to 5 was observed.

The structures of the two compounds (4 and 5) were determined on the basis of their spectral data [4 as a colorless liquid: $C_{12}H_{16}O_4$; m/e 224(M$^+$); ν_{max}(film) 3400br., 1620, and 1520cm^{-1};

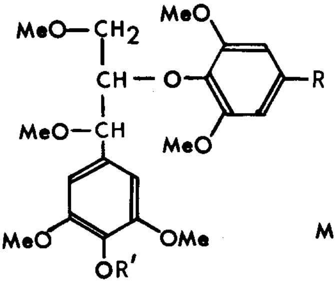
δ(CDCl$_3$) 3.31(3H, s), 3.89(6H, s), 4.54(1H, d, J= 6Hz), 5.18(1H, br.d, J= 10Hz), 5.25(1H, br.d, J= 17Hz), 5.55(1H, s, OH), 5.94(1H, ddd, J= 6,10,17Hz), and 6.58(2H, s). **5** as a colorless liquid: $C_{13}H_{18}O_5$; m/e 254(M^+); ν_{max}(film) 3400br., 1615, and 1520cm^{-1}; δ(CDCl$_3$) 3.19(6H, s), 3.89(6H, s), 5.46(1H, dd, J= 2,16Hz), 5.27(1H, dd, J= 2,10Hz), 5.67(1H, dd, J= 10,16Hz), and 6.70(2H, s)]. The third compound is a dimeric compound, whose tentative structure has been based on its spectral data coupled with some chemical evidences [mp 100-101°, $C_{24}H_{32}O_8$; m/e 448(M^+); ν_{max}(KBr) 3350br., 1615, 1590, 1520, and 1500cm^{-1}; δ(CDCl$_3$) 3.28(3H, s), 3.30(3H, s), 3.2-3.3(2H, superimposed on the two MeO signals), 3.52(1H, dd, J= 3,11Hz), 3.71(6H, s), 3.82 (6H, s), 3.7-3.8(1H, superimposed on the two MeO signals), 4.32(1H, m), 4.41(1H, d, J= 5.5Hz), 4.99(1H, br.d, J= 10Hz), 5.01(1H, br.d, J= 17Hz), 5.44(1H, s), 5.88(1H, m), 6.28(2H, s), and 6.53(2H, s)]. When treated with Ac_2O-pyridine (room temp., overnight), the dimer was converted into an acetate (**7**) [ν_{max}(film) 1765cm^{-1} and no OH band], which was further subjected to catalytic hydrogenation with PtO_2 in MeOH to give the corresponding dihydro compound (**8**) in a quantitative yield [$C_{26}H_{36}O_9$; m/e 492(M^+); δ(CDCl$_3$) 0.93(3H, t, J= 7.5Hz), 1.62(2H, br.sextet, J= 7.5Hz), 2.31(3H, s), and 2.50(2H, t, J= 7.5Hz)]. From the NMR and mass spectra of **6** and **8**, one of the two newly formed MeO groups must be located at the benzylic position [**6**, m/e 197 and δ4.41; **8**, m/e 239 and δ4.50(1H, d, J= 5.5Hz)]. The remaining one seems to be attached to the end of the side chain, as judged from δ-values assignable to the MeO-CH^{a}H^b-CH^c(OAr)- grouping [**6**, δ3.52(H^a), 3.7-3.8(H^b), and 4.32(H^c); **8**, δ3.55(H^a), 3.7-3.8(H^b), and 4.29(H^c)], although another possible structure with an ArO-CH$_2$-CH(OMe)- grouping is not necessarily ruled out.

According to the similar procedure as described earlier, the anodic oxidation of **3** was carried out in the neutral solution [MeOH-H$_2$O (9 : 1)] buffered with excess NaHCO$_3$ to give several oxidation products (**1**, **4**, **9**, **10**, **11a**, and **11b**) in 1, 3.1, 13, 1, 21, and 1.6% yields, respectively. Of these compounds, the physical data of the synthetic asatone (**1**) and **4** were completely identical with those of each authentic sample. The structures of two dienones (**9** and **10**) were also based on their spectral data [**9** as a colorless viscous liquid: $C_{12}H_{16}O_4$; m/e 224(M^+); ν_{max}(film) 1690, 1660, and 1625cm^{-1}; δ(CDCl$_3$) 2.51(2H, d, J= 7Hz), 3.17(3H, s), 3.69(6H, s), 5.05(1H, br.d, J= 16Hz), 5.09(1H, br.d, J= 11Hz), 5.59(2H, s), and 5.56-5.88(1H, m). **10** as a colorless viscous liquid: $C_{11}H_{14}O_4$; m/e 210(M^+); ν_{max}(film) 3300, 1660, and 1600cm^{-1}; δ(CDCl$_3$) 2.75(2H, d, J= 7Hz), 3.78(6H, s), 4.99(1H, br.d, J= 16Hz), 5.00(1H, br.d, J= 11Hz), 5.45(2H, s), and 5.23-5.57(1H, m)].

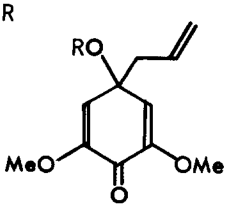
The two remaining compounds (**11a** and **11b**) are stereoisomers to each other, and their structures have also been elucidated on the basis of their spectral and chemical properties, except for their stereochemistry [**11a** as a colorless viscous liquid: $C_{24}H_{32}O_8$; m/e 448(M^+), 223, and 197; ν_{max}(film) 3425, 1740, 1610, and 1515cm^{-1}; δ(CDCl$_3$) 1.62(1H, dd, J= 3,8Hz), 1.62(1H, dd, J= 3,10Hz), 2.22(1H, ddd, J= 2,8,10Hz), 2.82(1H, dt, J= 2,3Hz), 2.98(2H, br.d, J= 6Hz), 3.22 (3H, s), 3.23(3H, s), 3.32(3H, s), 3.63(3H, s), 3.87(6H, s), 4.53(1H, d, J= 2Hz), 5.16(1H, br.d, J= 10Hz), 5.21(1H, br.d, J= 17Hz), 5.49(1H, s, OH), 5.83(1H, br.s), 5.85(1H, tdd, J= 6,10,17Hz), and 6.43(2H, s). **11b** as a colorless viscous liquid: $C_{24}H_{32}O_8$; m/e 448(M^+), 223, and 197; ν_{max}(film) 3425, 1740br., 1615, and 1520cm^{-1}; δ(CDCl$_3$) 1.46(1H, ddd, J= 3,6,13Hz), 1.99(1H, ddd, J= 3,10,13Hz), 2.51-2.94(4H, complex), 3.21(3H, s), 3.29(6H, s), 3.62(3H, s), 3.88(6H, s), 4.48 (1H, d, J= 5Hz), 4.87(1H, br.d, J= 16Hz), 4.92(1H, br.d, J= 10Hz), 5.15(1H, br.s), 5.26(1H, ddd,



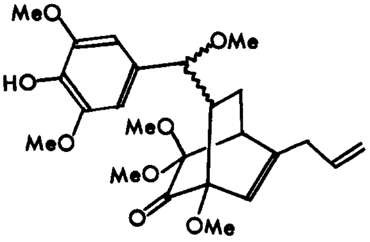
4 R = H
5 R = OMe



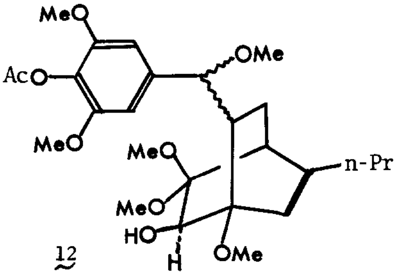
6 R = $CH_2CH=CH_2$, R'= H
7 R = $CH_2CH=CH_2$, R'= Ac
8 R = n-Pr, R'= Ac



9 R = Me
10 R = H



11a and 11b



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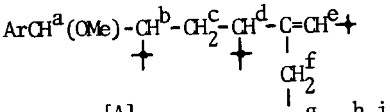


$$\mathrm{ArCH^{a}(OMe){-}\underset{|}{CH^{b}}{-}CH_{2}^{c}{-}\underset{|}{CH^{d}}{-}\underset{\underset{\underset{CH^{g}=CH_{2}^{h,i}}{|}}{\underset{|}{CH_{2}^{f}}}}{C}{=}CH^{e}{-}}$$

[A]

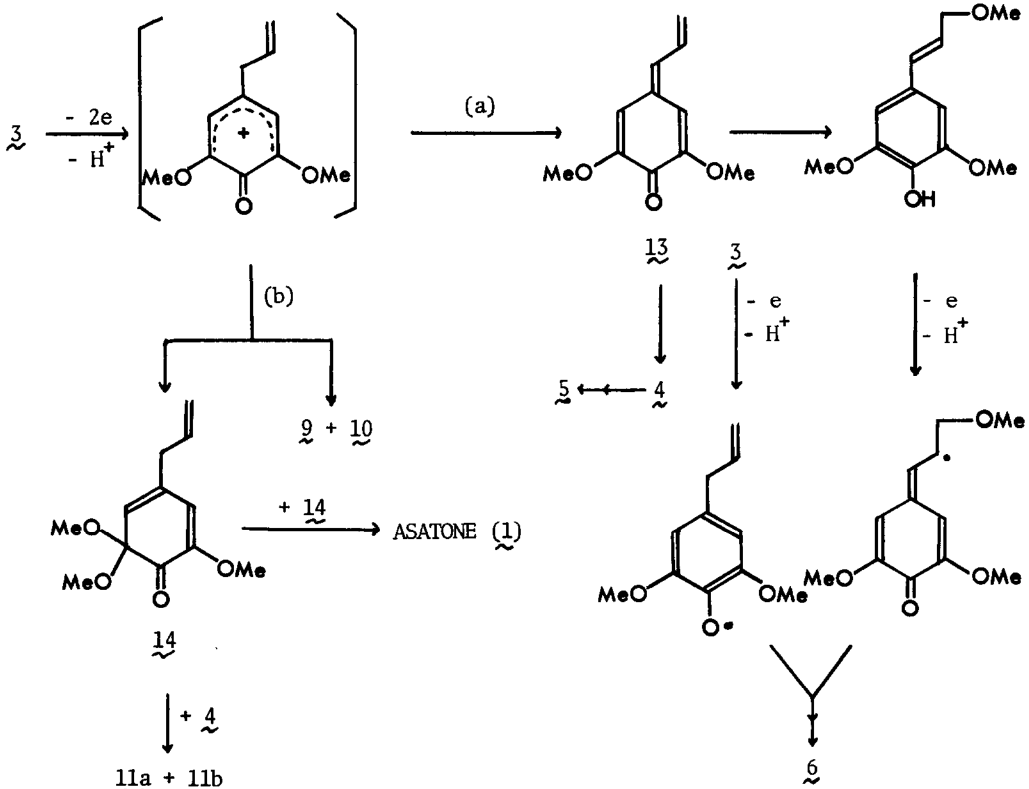
J= 6,10,16Hz), 5.50(1H, s, <u>OH</u>), and 6.50(2H, s)]. The presence of a partial structure [A] can be confirmed by analysis of the NMR spectrum of 11a with aid of double resonance experiments [δ 4.53(H^a), 2.22(H^b), 1.62(H^c), 2.82(H^d), 5.83(H^e), 2.98(H^f), 5.85(H^g), 5.16(H^h), and 5.21(H^i)]. Acetylation of 11a with Ac_2O-pyridine gave the corresponding acetate, which was further subjected to catalytic hydrogenation (PtO_2 in EtOAc) followed by $NaBH_4$ reduction in dioxane to afford a hydroxy compound (12) in high yields [$C_{26}H_{38}O_9$; m/e 494(M^+), 391, 239, and 197; ν_{max} (film) 3520, 1765, 1660(weak), 1605, and 1505cm^{-1}; λ_{max}(MeOH) 281, 270, 240sh, and 217nm (ε, 470, 670, 4230, and 8640, respectively); δ($CDCl_3$) 0.96(3H, t, J= 7Hz), 1.25(1H, dd, J= 3, 10Hz), 1.25(1H, dd, J= 3,8Hz), 1.51(2H, br.sextet, J= 7Hz), 2.0-2.2(3H, complex), 2.30(3H, s), 2.48(1H, m), 3.13(3H, s), 3.20(3H, s), 3.23(3H, s), 3.39(1H, s, <u>OH</u>), 3.54(3H, s), 3.67(1H, s), 3.80(6H, s), 4.57(1H, d, J= 2Hz), 5.80(1H, br.s), and 6.50(2H, s)]. The NMR spectrum of 12 indicates the presence of a n-propyl group instead of the allyl group in 11a. Furthermore, the NMR singlet at δ3.67 indicates that there is no hydrogen atom at α and α'-positions of the CO group (ν_{max} 1740cm^{-1}) in 11a. Finally, the mass spectrum of 11a has two remarkable peaks at m/e 223 and 197. The fragment ion at m/e 223 must be formed by retro-Diels-Alder reaction of 11a on electron impact. The peak at m/e 197 is due to the ArCH(OMe)- grouping in [A]. In fact, a new peak was observed at m/e 239 in the case of the acetylation product (12). From these data, one of the two dimers must be depicted as 11a, except for its stereochemistry. The remaining one (11b) must also have the same carbon skeleton as that of 11a from its spectral data

We further examined the anodic oxidation of 3 in the neutral media buffered with excess $NaHCO_3$, using an undivided cell different from the two-compartment one. In this case, asatone (1) was also produced, in 3.3% yield, in addition to the other known compounds (9, 10, 11a and

11b).

In conclusion, the formation process of these oxidation products is shown in Scheme 1. On anodic oxidation in the basic media, clearly, one of the two hydrogen atoms at the benzylic position is easily lost to afford an extended methylene quinone (13), from which 4, 5, and 6 are formed. Interestingly, the oxidation products (1, 9, 10, 11a, and 11b) have not been detected by HPLC. On the other hand, in the case of the neutral media, path (b) is more favorable than path (a). Thus, as already been expected from the biogenesis of asatone (1) and isoasatone (2),[1] asatone could be synthesized from 2,6-dimethoxy-4-allylphenol (3) through an intermediate (14).

Scheme 1. Anodic oxidation of 2,6-dimethoxy-4-allylphenol (3)



References and Footnotes

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3. The high performance liquid chromatography (HPLC) was carried out at 20 ± 0.1°, using Polymer HP-255 (ϕ 3mm x 50cm) [solvent system: MeOH-H_2O (97 : 3); flow rate: 0.75ml/min].