Structure and Synthesis of Diphyllin

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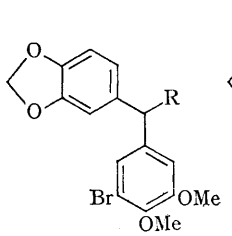
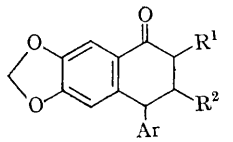
DIPHYLLIN, a phenolic lignan lactone isolated from *Diphylleia grayi*, was reported, by Murakami and Matsushima,[1] to have structure (I), and its methyl ether was found by Munakata *et al.*[2] to be identical with justicidin A, a fish poison isolated from *Justicia Hayatai var. decumbens*. Govindachari *et al.*[3] reported an isolation of diphyllin from *Cleistanthus collinus* (*Roxb.*) *Benth & Hook. f.* and proposed a revised structure (II) on chemical evidence. We now report the syntheses of compounds (I) and (II), and their non-identity with diphyllin. We propose, on the basis of its synthesis, that diphyllin has the structure (III).

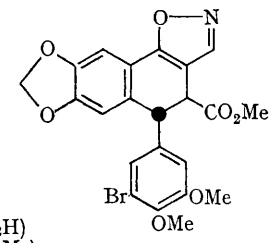
The diphenylmethanol (IV), prepared by reduction of 3-bromo-4,5-dimethoxy-3′,4′-methylenedioxybenzophenone, was brominated, condensed with diethyl sodioacetosuccinate, and hydrolysed to give an isomeric mixture of the diphenylmethylsuccinic acid (V), whose anhydride was cyclized with stannic chloride to the *cis*- and *trans*-oxotetralincarboxylic acid (VI) [characterized as methyl esters (VIIa) and (VIIb)]. The position of ring closure is evident from absence of *ortho*-coupling of the aromatic protons in the n.m.r. spectra in $CDCl_3$: (VIIa), τ 3·54 (d, J 2·5), 3·31 (d, J 2·5 c./sec.), 3·43 (s), and 2·47 (s); (VIIb), τ 3·39 (d, J 2·5), 3·14 (d, J 2·5 c./sec.), 3·58 (s), and 2·47 (s). The *trans*-ester (VIIb) was condensed with methyl formate and then with hydroxylamine to give an isoxazole (VIII) which on lithium aluminium hydride reduction at −60° and subsequent treatment with sodium ethoxide was



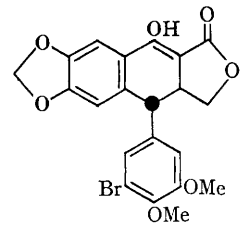
(IV) R=OH
(V) R=CH·COOH
CH_2·COOH



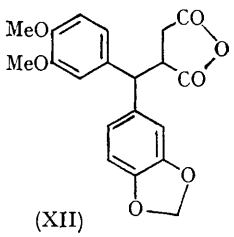
(VI; R^1=H, R^2=CO_2H)
(VIIa, b; R^1=H, R^2=CO_2Me)
(IX ; R^1=CN, R^2=CH_2OH)
Ar=bromodimethoxybenzene



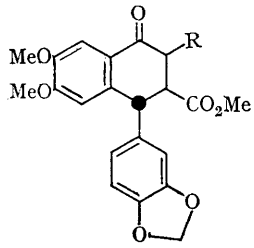
(VIII)



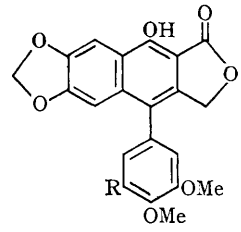
(X)



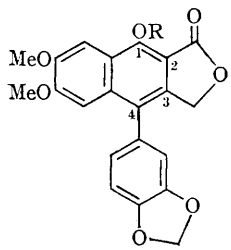
(XII)



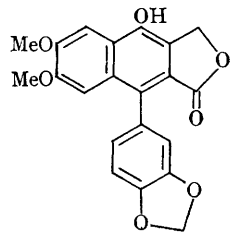
(XIII; R=H)
(XV; R=CHO)



(I; R=H)
(XI; R=Br)



(II; R=H)
(XIV; R=Me)



(III)

converted into an α-cyano-tetralone (IX), m.p. 205—208°, ν_{max}(KBr) 3401(OH), 2232(C≡N), and 1672(C=O) cm.$^{-1}$. On treatment with hydrogen chloride in absolute ethanol, (IX) gave a γ-lactone (X), (61%) m.p. 199—201°, ν_{max}(KBr) 3367(OH), 1776(C=O), and 1661(C=O, medium) cm.$^{-1}$, which was dehydrogenated with selenium dioxide in boiling acetic acid to a naphthol (XI), (67%) m.p. 165—168°, ν_{max}(KBr) 3344(OH), 1727(C=O), and 1626(arom.)cm.$^{-1}$. On hydrogenation over Raney nickel in dimethylformamide in the presence of potassium hydroxide, (XI) gave quantitatively the debromonaphthol (I), m.p. 272—275°, ν_{max}(KBr) 3368(OH), 1724(C=O), 1626, 1604, and 1578(arom.)cm.$^{-1}$. Compound (II), m.p. 215—217°, ν_{max}(KBr) 3369(OH), 1709(C=O), 1631, and 1617(arom.)cm.$^{-1}$, was synthesized as follows. Cyclization of a diphenylmethylsuccinic anhydride (XII), prepared by sodium amalgam reduction of 3,4-dimethoxy-3′4′-methylenedioxydiphenylmethylidenesuccinic acid[4] and subsequent dehydration with acetyl chloride, with stannic chloride in nitrobenzene gave two isomeric *trans*-oxo-tetralincarboxylic acids in 3% and 42% yield. The methyl ester of the minor isomer was identical with the tetralone derived from (VIIb) by hydrogenolysis. The methyl ester (XIII) of the major isomer was converted to (II) by a similar 6-step procedure to that for the synthesis of (XI) given above.

Compounds (I) or (II) both showed a positive ferric chloride test, and were shown from i.r. and t.l.c. not to be identical with diphyllin, [lit.,[1] m.p. 291°, ν_{max}(Nujol) 3220, 1709, and 1613 cm.$^{-1}$, a negative ferric chloride test]. The methyl ether (XIV), m.p. 264—267°, ν_{max}(KBr) 1740(C=O), 1617, and 1604(arom.)cm.$^{-1}$, shows a lactone methylene signal at τ 4·92 ($CDCl_3$) in the n.m.r. spectrum,which is strongly shielded (*cf.* justicidin A, lit.,[2] τ 4·48), suggesting that the lactone methylene in diphyllin or justicidin A is not located at C-3 and that the structure of diphyllin should be revised to (III). The synthesis of (III) was achieved by 3-step procedure consisting of catalytic reduction of the formyltetralone (XV) followed by lactonization and dehydrogenation with selenium dioxide. Compound (III), m.p. 285—289°, ν_{max}(KBr) 3175(OH), 1698(C=O), and 1613 (arom.)cm.$^{-1}$, was shown to be completely identical with diphyllin from i.r. (KBr) and t.l.c. measurements.

We thank Professor T. Murakami for providing the sample and i.r. spectrum of diphyllin.

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[2] K. Munakata, S. Marumo, K. Ohta, and Y. L. Chen, *Tetrahedron Letters*, 1965, 4167.
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