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THE SYNTHESES OF JUSTICIDIN B AND RELATED COMPOUNDS

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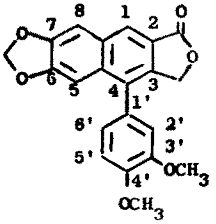
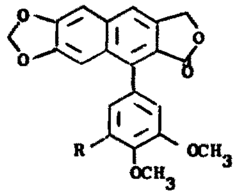
The structure of justicidin B, a fish killing agent, isolated from <u>Justicia Hayatai</u> var. <u>decumbens</u> has been tentatively assigned as (I).1) The previous evidence upon 4-phenylnaphthalene lactone (lignan lactone) skeleton was obtained from the close similarity on the UV spectrum of justicidin B to that of dehydroanhydropicropodophyllin (II). The orientation of the lactone ring and locations of methoxyl and methylenedioxy groups were concluded relating to justicidin A, the structure2) of which was proved to be identical with diphyllin methyl ether.1) However, the possibility that exchanged the positions of methoxyls and methylenedioxy *vice versa* could not be eliminated.

This report describes the syntheses of compounds (I) (III) (IV), and justicidin B was finally concluded to have the structure (III).

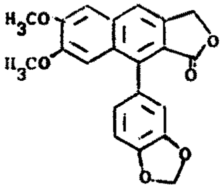


(I)



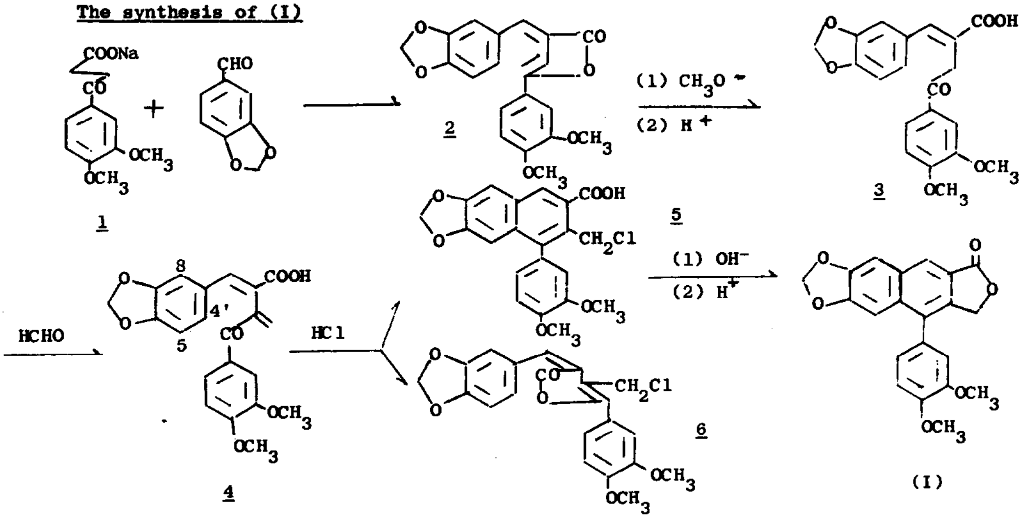
(II) $R = OCH_3$

(IV) $R = H$



(III)

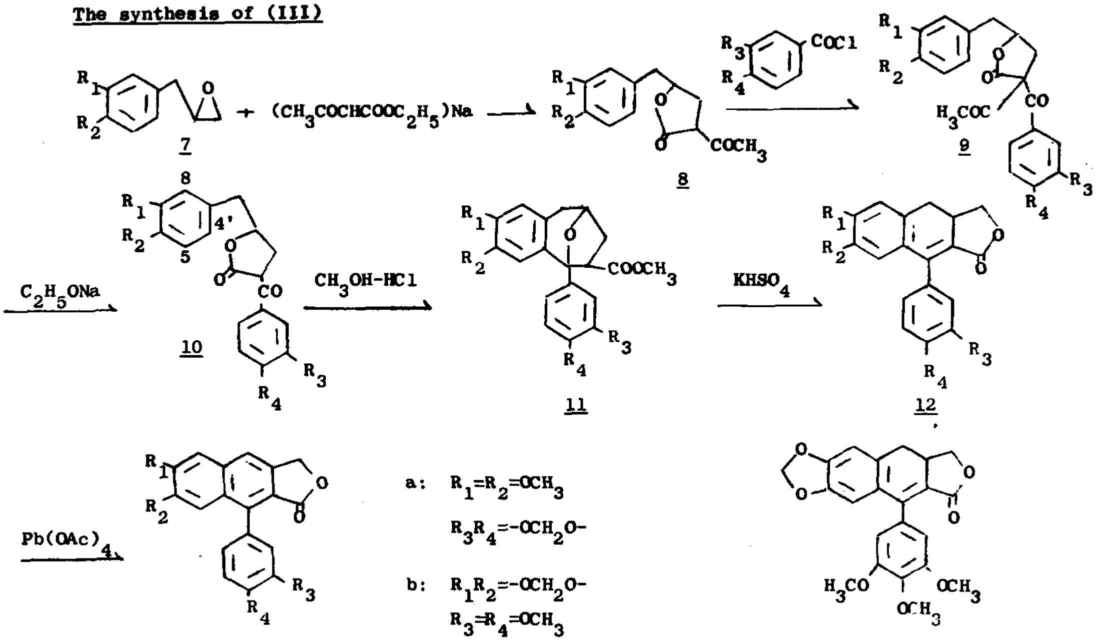
The synthesis of (I)



The synthesis was carried out according to the method of Haworth et al[3] for the synthesis of dehydromethylconidendrin.

Sodium β-3,4-dimethoxybenzoyl propionate[4] 1 was condensed with piperonal in acetic anhydride to afford 2,[5] mp 234°, ν^{KBr} 1770 cm^{-1}, $\lambda_{max}^{CHCl_3}$ 242, 263, 270, 290 and 420 mμ (log ε 4.18, 4.30, 4.30, 4.10 and 4.66), yield 69 %. Saponification of 2 with sodium methoxide, followed by acidification, gave 3, mp 238°, ν^{KBr} 1670 cm^{-1}(broad), $\lambda_{max}^{CHCl_3}$ 240, 280 and 310 mμ (log ε 4.28, 4.31 and 4.34), yield 62 %. The close similarity of the UV spectrum to that of the equimolar mixture of 3,4-dimethoxybenzoylpropionic acid and p-methoxycinnamic acid indicated that 1 was condensed with piperonal at α-position to the carboxylate. Aldol condensation of 3 with formalin yielded 4, mp 175°, ν^{KBr} 1660, 1645, 1625 and 880 cm^{-1}, $\lambda_{max}^{CH_3OH}$ 230, 290 and 317 mμ (log ε 4.46, 4.28 and 4.35), yield 73 %. An excess of conc. hydrochloric acid was added into the acetic acid solution of 4 and the solution was kept at room temperature for 3 days, thus, 5, mp 230°, ν^{KBr} 1682 cm^{-1}, $\lambda_{max}^{CH_3OH}$ 262 and 285 mμ (log ε 4.60 and 3.97), yield 48 %, was precipitated together with almost equal amount of 6, mp 215°, which could be separated by recrystallization from acetone. The NMR spectrum[6] of methyl ester of 5 showed a pair of doublets coupled in 6.0 cps at δ 6.82 ($C_{6'}$-H) and 7.02 ppm ($C_{5'}$-H) and five singlets of aromatic protons at δ 6.70(broad,$C_{2'}$-H),6.88(C_5-H),7.16 (C_8-H) and 8.31 ppm (C_1-H), proving that the ring fusion occurred at $C_{4'}$-position. (I) was quantitatively produced from 5 by hydrolysis with boiling 10 % aqueous sodium hydroxide, followed by lactonization. It has mp 280°, ν^{KBr} 1760 cm^{-1}, $\lambda_{max}^{CHCl_3}$ 250, 260, 315 and 350 mμ (log ε 4.52, 4.52, 3.94 and 3.56).

The synthesis of (III)



a: $R_1=R_2=OCH_3$
$R_3R_4=-OCH_2O-$

b: $R_1R_2=-OCH_2O-$
$R_3=R_4=OCH_3$

(III) $R_1=R_2=OCH_3$, $R_3R_4=-OCH_2O-$

(IV) $R_1R_2=-OCH_2O-$, $R_3=R_4=OCH_3$

The synthesis was carried out by the modified method of Schrecker and Hartwell[7] for the synthesis of dehydroanhydropicropodophyllin.

Condensation of methyleugenoloxide[8] 7a with sodium ethylacetoacetate gave 8a, oil, ν^{KBr} 1725 and 1760 cm^{-1}, $\lambda_{max}^{CH_3OH}$ 230 and 278 mμ (log ε 3.95 and 3.60), yield 35 %. 8a was condensed with piperonyloyl chloride in benzene, giving 9a, mp 132°, ν^{KBr} 1770, 1720 and 1665 cm^{-1}, $\lambda_{max}^{CH_3OH}$ 230, 278 and 315 mμ (log ε 4.46, 4.06 and 4.05), yield 86 %. Deacetylation of 9a with equimolar sodium ethoxide yielded 10a, mp 159°, ν^{KBr} 1750 and 1663 cm^{-1}, $\lambda_{max}^{CH_3OH}$ 230, 278 and 315 mμ (log ε 4.56, 4.16 and 4.13), yield 77 %. Boiling of 10a in methanol saturated with hydrogen chloride gave 11a, mp 132°, ν^{KBr} 1710 cm^{-1}, $\lambda_{max}^{CH_3OH}$ 225, 245 and 305 mμ (log ε 4.34, 4.24 and 4.11), yield 32 %. Evidence that the ring fusion occurred at $C_{4'}$ and not $C_{8(5)}$ was obtained from the NMR spectrum of 11a which showed a pair of doublets coupled in 6.0 cps at δ 6.60 ($C_{6'}$-H) and 6.69 ppm ($C_{5'}$-H) and three singlets of aromatic protons at δ 6.36(C_5-H), 6.55(broad,$C_{2'}$-H) and 6.76 ppm(C_8-H). The seven membered ring system having an ether linkage was proved by observing that, in the IR spectrum, no hydroxyl absorption was found and, in the NMR spectrum, one proton of multiplet was detected at δ 4.56 ppm which should be assigned to the methine proton bearing the ether oxygen, thus, excluding the alternative structure.[9] Heating 11a with potassium hydrogen sulfate at 180°, 12a was produced through the ring construction and subsequent dehydration. 12a has mp 201°, ν^{KBr} 1740 cm^{-1}, yield 54 %. The UV spectrum, $\lambda_{max}^{CH_3OH}$ 247, 310 and 345 mμ (log ε 4.32, 3.94 and 4.12) was almost same as that of γ-apopicropodophyllin (V).10) (III) was produced from 12a in 35 % yield by oxidizing it with lead tetraacetate in acetic acid. (III) had mp 247°, ν^{KBr} 1760 cm^{-1} and $\lambda_{max}^{CHCl_3}$ 260, 295, 310 and 350 mμ (log ε 4.78, 4.02, 4.02, 3.73). The synthetic sample was found to be completely identical with natural justicidin B on the respects of the IR, UV and NMR spectra, thin layer chromatogram, the mixture melting point and the biological activity.

The synthesis of (IV)

The synthesis of (IV) was carried out by the same procedure employed to (III), in that case the starting materials used were safroloxide (7b) and veratoroyl chloride. The IR and UV spectra of each compound were closely similar to those of a series.

Acknowledgement

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References

1) K.Munakata, S.Marumo, K.Ohta and Y.Chen, Tetrahedron Letters, No 47, 4167 (1965).

2) The further investigation of justicidin A will be reported separately.

3) R.D.Haworth, T.Richardson and G.Scheldrick, J.Chem.Soc., 1576 (1935).

4) M.H.Haq, M.L.Kapur and J.N.Ray, J.Chem.Soc., 1088(1933).

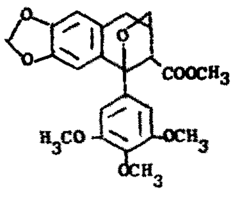
5) Satisfactory elemental analyses were obtained for all compounds synthesized.

6) NMR spectra were measured at 60 Mc. using tetramethylsilane as an internal standard and $CDCl_3$ as a solvent for all compounds synthesized, except 11a which was measured at 100 Mc..

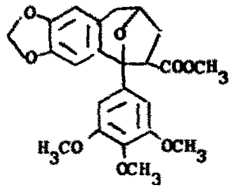
7) A.W.Shrecker and J.L.Hartwell, J.Am.Chem.Soc., **74** 5672 (1952)

8) Fourneau and Tiffeneau, Compt. rend., **140**, 1595 (1905); **141**, 662 (1905).

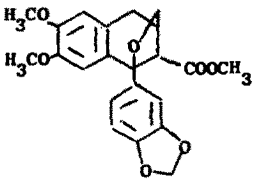
9) On the synthesis of dehydroanhydropicropodophyllin, A.W.Schrecker and J.L.Hartwell obtained in the analogous reaction two products, the structures of which were assumed to be either of the isomer (i) or (ii). However, in our studies only one product 11a was obtained, and the possibility of (iii) was denied from the NMR consideration.



(i)



(ii)



(iii)

10) A.W.Schrecker and J.L.Hartwell, *J.Am.Chem.Soc.*, **74** 5676 (1952).