Tetrahedron, 1961, Vol. 14, pp. 275 to 283. Pergamon Press Ltd. Printed in Northern Ireland

THE STRUCTURE OF PSORALIDIN

H. N. KHASTGIR, P. C. DUTTAGUPTA and P. SENGUPTA
The Research Division, East India Pharmaceutical Works Ltd., Calcutta-34, India

(*Received* 15 *February* 1961)

Abstract—Psoralidin, $C_{20}H_{16}O_5$ the phenolic coumarin of *Psoralea corylifolia* Linn. has been shown to possess two hydroxyl groups, one conjugated δ-lactone, one isopentenyl group and an intramolecular ether linkage. On systematic degradation dihydropsoralidin dimethyl ether gave 2-hydroxy-4-methoxybenzaldehyde and 2,4-dimethoxy-5(-3-methylbutyl)-benzoic acid. The synthesis of the latter compound has been described. On the basis of the degradation experiments coupled with ultra-violet and infra-red absorption data, the structure of psoralidin has been established as 6-(3-methylbut-2-enyl)-coumestrol (IV, R = H).

PREVIOUSLY we have identified[1a] the sterol of the seeds of *Psoralea corylifolia* Linn. as stigmasterol and have shown[1b] that the furocoumarins psoralen and isopsoralen can be isolated from the glycosidic fraction of the seed kernel. The present communication deals with the structure elucidation of the phenolic coumarin, psoralidin, first isolated from the pericarp of the seeds of *P. corylifolia* by Chakravarti *et al.*[2] and assigned the molecular formula $C_{16}H_{14}O_4$. This group of workers suggested the presence of a phenolic hydroxyl group, a lactone group and an isopentenyl group in the molecule of psoralidin. Acetone was isolated from the chromic acid oxidation of psoralidin. On the basis of these findings, these workers suggested[2] the provisional structure IA for the coumarin.

By following the scheme for isolation outlined by Chakravarti *et al.*[2] we failed to isolate psoralidin from the pericarp of the seeds. Nevertheless, we have been able to isolate from the phenolic fraction of the alcoholic extract of the seed kernel, a crystalline compound, m.p. 290–292°d in 0·16 per cent yield, which was identified[3] as psoralidin by direct comparison of its methyl ether, m.p. 190–191° with psoralidin methyl ether, m.p. 190° of Chakravarti *et al.*[4] (mixed m.p., infra-red and paper chromatography[5]).

Since the ultra-violet absorption spectra of the acetate of a phenolic coumarin is identical with that of the corresponding desoxycoumarin,[6] we first tried to compare the ultra-violet absorption spectra of psoralidin acetate with that of psoralen IB. The vast difference between the spectra of the two compounds makes the structure IA of Chakravarti *et al.* for psoralidin untenable. So we thought it desirable to make a systematic investigation on the structure of psoralidin. We observed[3] that psoralidin has the molecular formula $C_{20}H_{16}O_5$ and not $C_{16}H_{14}O_4$ as suggested by Chakravarti *et al.*, from the consideration of the analytical data and molecular weight of its methyl ether. The presence of two phenolic hydroxyl groups is indicated by the analysis of the methyl ether, which shows the presence of two methoxy groups, whereas psoralidin

[1] H. N. Khastgir, P. C. Duttagupta and P. Sengupta, *Ind. J. Appl. Chem. a* **22**, 35 (1959); *b* **22**, 82 (1959).
[2] K. K. Chakravarti, A. K. Bose and S. Siddiqui, *J. Sci. & Ind. Res. India* **7B**, 24 (1948).
[3] P. C. Duttagupta, H. N. Khastgir and P. Sengupta, *Chem. & Ind.* [a] 48 (1960); [b] 937 (1960).
[4] We are highly indebted to Dr. K. K. Chakravarti for the gift of a sample of their psoralidin methyl ether.
[5] We are highly indebted to Dr. D. P. Chakraborty of Bose Institute, Calcutta for the paper chromatographic analysis.
[6] T. Nakabayashi, T. Tokorayama, H. Miyazaki and S. Isono, *J. Pharm. Soc. Japan* **73**, 669 (1953); *Chem. Abstr.* **47**, 10348[c] (1953).

shows the presence of none. Further psoralidin forms a diacetate,[3] $C_{24}H_{20}O_7$, m.p. 221–223° (reported,[2] m.p. 220°).

The infra-red spectra of psoralidin in KBr disk show peaks at 3350 (phenolic hydroxyl), 1710 (conjugated δ-lactone), 1625 (conjugated C=C), 1600, 1578 and 1498 (aromatic nucleus) and 1261 cm^{-1} (aromatic C—O[7,8]).

Psoralidin dimethyl ether does not show any hydroxyl peak in the infra-red spectra but shows peaks at 1732 (conjugated δ-lactone), 1638 (conjugated C=C), 1604, 1570 and 1500 (aromatic nucleus) and 1261 cm^{-1} (aromatic C—O). Psoralidin diacetate shows infra-red peaks at 1740 (acetate and lactone), 1625 (conjugated C=C), 1600, 1575 and 1498 (aromatic nucleus) and 1225 cm^{-1} (acetate). Thus of the five oxygen atoms of psoralidin, two are present in two phenolic hydroxyl groups and two in a conjugated δ-lactone group. The fifth oxygen atom is present as an ether,[3] as shown by the peaks at 1261 and 1094 cm^{-1} in the infra-red spectra of psoralidin.

The ultra-violet absorption spectra of psoralidin show peaks at 208, 244, 305 and 347 mμ (Table 1). Psoralidin dimethyl ether shows similar spectra, whereas psoralidin

TABLE 1. ULTRA-VIOLET ABSORPTION DATA*

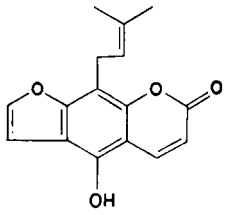
Psoralidin	λ_{max}	208 (40,800), 244 (20,300), 305 (7000) and 347 mμ (25,300)
Psoralidin dimethyl ether	λ_{max}	208 (42,600), 243 (24,000), 304 (8500) and 344 mμ (28,500)
Wedelolactone[13]	λ_{max}	211 (37,400), 250 (19,200), 303 (8200) and 350 mμ (22,700)
Wedelolactone trimethyl ether[10]	λ_{max}	247 (18,620), 300 (6300) and 350 mμ (22,400)
Coumestrol[12]	λ_{max}	244 (—), 304 (—) and 343 mμ (—)

* ε values are given in parentheses

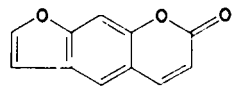
diacetate shows maxima at 207, 225 300 and 330 mμ. The ultra-violet absorption spectra of psoralidin and its dimethyl ether are so strikingly similar to those of wedelolactone (II)[9,10] and coumestrol (III)[11,12] that we were led to believe that psoralidin has the same skeletal structure as that of these two compounds. Finally we have been able to establish[3b] that psoralidin is in fact 6-(3-methylbut-2-enyl)-coumestrol (IV, R = H) following the series of reactions described below.

Psoralidin (IV, R = H) and its dimethyl ether (IV, R = Me) smoothyl absorbed one mole of hydrogen in presence of palladium on charcoal catalyst to yield dihydropsoralidin (V, R = H), m.p. 274–276° and dihydropsoralidin dimethyl ether (V, R = Me), m.p. 193–195° respectively. The ultra-violet absorption spectra of the dihydro-compounds are similar to those of psoralidin and its dimethyl ether, thus establishing the presence of a non-conjugated ethylenic linkage in the molecule of

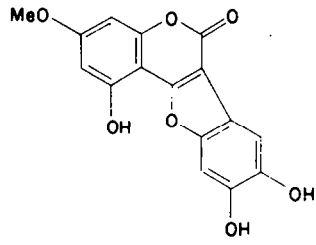
[7] O. A. Stamm, H. Schmid and J. Buchi, *Helv. Chim. Acta* **41**, 2006 (1958).
[8] J. Eisenbeiss and H. Schmid, *Helv. Chim. Acta* **42**, 61 (1959).
[9] T. R. Govindachari, K. Nagarajan, B. R. Pai and P. C. Parthasarathy, *J. Chem. Soc.* 545 (1957).
[10] T. R. Govindachari, K. Nagarajan and P. C. Parthasarathy, *J. Chem. Soc.* 548 (1957).
[11] E. M. Bickoff, R. L. Lyman, A. L. Livingston and A. N. Booth, *J. Amer. Chem. Soc.* **80**, 3969 (1958).
[12] L. Jurd, *J. Org. Chem.* **24**, 1786 (1959).
[13] We are highly indebted to Prof. T. R. Govindachari, Presidency College, Madras for the gift of a sample of wedelolactone.



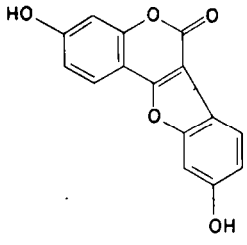
I A



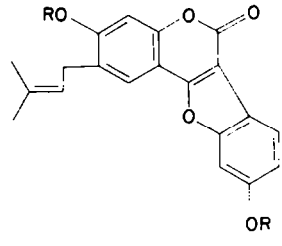
I B



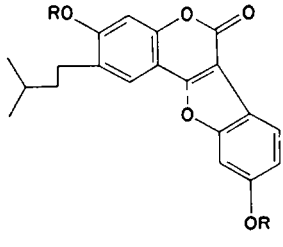
II



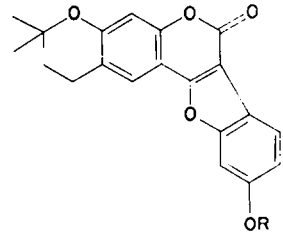
III



IV



V



VI

psoralidin. On repeating the chromic acid oxidation experiment[2] on psoralidin dimethyl ether, we also have been able to isolate acetone (identified as its 2,4-dinitrophenyl hydrazone). This experiment establishes the presence of the group $(CH_3)_2{\cdot}C{=}C$ in psoralidin. Further, dihydropsoralidin on treatment with fuming nitric acid gives isocaproic acid, identified be paper chromatography.[5] This experiment confirms the presence of the group $(CH_3)_2{\cdot}C{=}CH{\cdot}CH_2{-}$ directly attached to the aromatic nucleus,

as originally suggested by Chakravarti *et al.*[2] On treatment with methanolic hydrochloric acid, psoralidin undergoes isomerization to the monohydroxy chroman (VI, R = H), m.p. 284–287°, having identical ultra-violet asborption spectra with those of psoralidin. The chroman (VI, R = H) forms a monomethyl ether (VI, R = Me), m.p. 172–174° and 197–200°. The formation of the chroman (VI, R = H), which we name isopsoralidin establishes[14] that the isopentenyl group must be situated at the *ortho*-position to one of the two phenolic hydroxyl groups in psoralidin.

On fusion with potassium hydroxide, psoralidin gives,[3] as expected, resorcinol and β-resorcylic acid (identified as its methyl ester). The presence of a coumarin type structure is demostrated by the fact that on treating psoralidin dimethyl ether (IV, R = Me) alternately with methanolic alkali and dimethyl sulphate, methyl psoralidinate trimethyl ether (VII), m.p. 114–115° is isolated. The infra-red spectra of this ester show a peak at 1705 cm^{-1} (conjugated ester) and the ultra-violet absorption spectra show maxima at 206, 229 and 325 mμ.

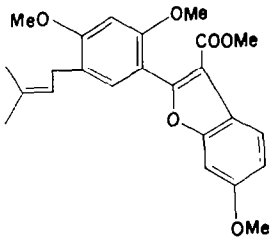
Similar treatment of dihydropsoralidin dimethyl ether (V, R = Me) with alkali and dimethyl sulphate yields methyl dihydropsoralidinate trimethyl ether (VIII, R = Me) as an oil, which on saponification affords[3] dihydropsoralidinic acid trimethyl ether (VIII, R = H), m.p. 197–198°d, having ultra-violet absorption maxima at 212 and 319 mμ. The latter compound on sublimation in vacuum smoothly eliminates a molecule of carbon dioxide and forms the decarboxy-compound (IX), m.p. 84–86°, which does not show any carbonyl peak in the infra-red spectra, but shows peaks at 1620 (C=C), 1582 and 1496 (aromatic nucleus), 1264 (aromatic C—O), 1110 (aromatic ether) and 1035 cm^{-1} (OMe).[8]

The decarboxy derivative (IX) on treatment with osmium tetroxide is expected to give the diol (X). But instead of the diol, we have been able to isolate only a light yellow crystalline compound, $C_{22}H_{28}O_6$, m.p. 113–115° to which we assign the benzoin structure (XI) on the following grounds. The compound is soluble in alkali and gives blue-violet colouration with alcoholic ferric chloride. The ultra-violet absorption spectra show maxima at 212, 230, 279 and 326 mμ and the infra-red spectra show peaks at 3500 (hydroxyl), 1635 (conjugated carbonyl) and 1605, 1575 and 1498 cm^{-1} (aromatic nucleus). It may be presumed that the benzoin (XI) has been formed through the intermediate hemiketal (X), which we have failed to isolate.

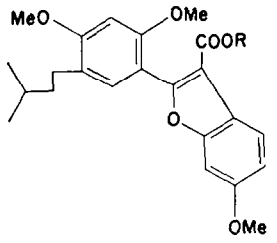
The benzoin (XI) was next oxidized with sodium periodate to yield 2-hydroxy-4-methoxybenzaldehyde (identified by paper chromatography of its 2,4-dinitrophenyl hydrazone[5]) and an acid, m.p. 90–91°, which was found to be identical (mixed m.p. and infra-red) with 2,4-dimethoxy-5-(3-methylbutyl)-benzoic acid (XII), synthesized by us by an unambiguous method described below.

Friedel-Craft's reaction between methyl β-resorcylate and isovaleryl chloride afforded methyl 2,4-dihydroxy-5-isovaleryl benzoate (XIII, R = H), m.p. 72–74° which was previously prepared[15] by the hydrogenation of methyl 2,4-dihydroxy-5-($\beta\beta$-dimethyl acrylyl)-benzoate. The dimethyl ether (XIII, R = Me), m.p. 129–130° of the phenolic keto-ester (XIII, R = H) on catalytic hydrogenation[16] in presence of perchloric acid gave an oily ester, which was directly saponified to give the acid (XII) m.p. 90–91°.

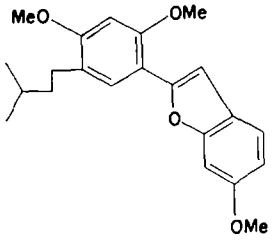
[14] P. Yates and G. H. Stout, *J. Amer. Chem. Soc.* **80**, 1694 (1958).
[15] J. Nickl, *Chem. Ber.* **92**, 1989 (1959).
[16] K. W. Rosenmund, E. Karg and F. K. Marcus, *Ber. Dtsch. Chem. Ges.* **75B**, 1850 (1942).



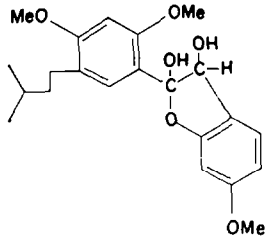
VII



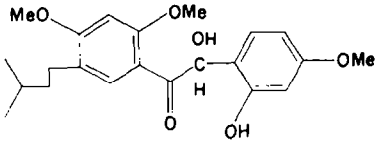
VIII



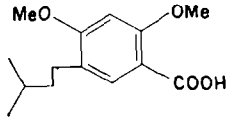
IX



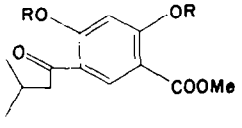
X



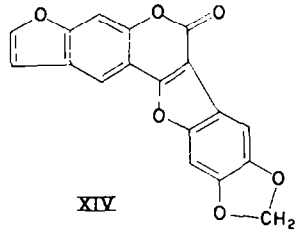
XI



XII



XIII



XIV

Thus psoralidin (IV, R = H) is a new addition to the family of benzfuranocoumarins of which wedelolactone (II), coumestrol (III) and erosnin (XIV)[8] were the pre-previously known members.

EXPERIMENTAL

The ultra-violet absorption spectra were measured in 95% ethyl alcohol and the infra-red spectra were measured in chloroform unless otherwise stated.

Isolation of psoralidin (IV, R = H)

1·5 Kg of defatted and powdered seed-kernel[1b] of *P. corylifolia* was extracted for 20 hr with 95% ethyl alcohol in a Soxhlet. The residue, obtained after the removal of ethanol was taken up in ether and extracted with cold 5% aqueous NaOH. The alkaline layer was acidified with cold dil HCl and

the precipitated material reextracted with ether, washed with water and dried (Na_2SO_4). On careful concentration, crude psoralidin (2·47 g, 0·16% yield on seed-kernel), m.p. 283–288°d was obtained. Repeated crystallization from acetone afforded the analytical sample of psoralidin (IV, R = H), m.p. 290–292°d R_f 0·78[17] (Reported[3] m.p. 315°d). It shows violet fluorescence in dil ethanolic solution (Found: C, 71·12; H, 4·93. $C_{20}H_{16}O_5$ requires: C, 71·42; H, 4·80%).

U.V. (a) See Table 1.

(b) In 0·1 N KOH in EtOH... λ_{max} 256 (ε 14,700), 285 (ε 18,500) and 395 mμ (ε 26,900).

I.R. (KBr) Peaks at 3350 (hydroxyl), 1710 (conjugated δ-lactone), 1625 (conjugated C=C), 1600, 1578 and 1498 (aromatic nucleus) and 1261 and 1094 cm^{-1} (aromatic C—O).

Psoralidin dimethyl ether (IV, R = Me)

A mixture of psoralidin (0·5 g), anhydrous potassium carbonate (4 g), dimethyl sulphate (4 cc) and acetone (60 cc) was refluxed for 5 hr. The crude solid isolated in the usual manner on crystallization from acetone gave psoralidin dimethyl ether (IV, R = Me; 0·4 g), m.p. 190–191°, R_f 0·63,[17] identical with the psoralidin methyl ether of Chakravarti *et al.* (mixed m.p., infra-red and paper chromatography). It shows violet fluorescence in dil ethanolic solution. (Found: C, 72·34; H, 5·68; OMe, 17·67. $C_{22}H_{20}O_5$ requires: C, 72·51; H, 5·53; OMe (two), 17·04%).

Mol. Wt. Found (Rast), 352. Calc., 364.

U.V. (a) See Table 1.

(b) In 0·1 N KOH in EtOH... λ_{max} 224 (ε 27,800), 304 (ε 7200) and 345 mμ (ε 11,200).

I.R. Peaks at 1732 (conjugated δ-lactone), 1638 (conjugated C=C), 1604, 1570 and 1500 (aromatic nucleus) and 1261 cm^{-1} (aromatic C—O).

Psoralidin diacetate (IV, R = Ac)

Psoralidin (75 mg) was acetylated in the usual manner with acetic anhydride (2 cc) and pyridine (2 cc). The crude solid on crystallization from ethyl acetate afforded psoralidin diacetate (IV, R = Ac), m.p. 221–223°. (Reported[3] m.p. 220°). (Found: C, 68·06; H, 4·89. $C_{24}H_{20}O_7$ requires: C, 68·56; H, 4·80%).

U.V. λ_{max} 207 (ε 39,900), 225 (ε 30,100), 300 (ε 13,650) and 330 mμ (ε 24,000).

I.R. Peaks at 1740 (acetate and lactone), 1625 (conjugated C=C), 1600, 1575 and 1498 (aromatic nucleus) and 1225 cm^{-1} (acetate).

Isopsoralidin (VI, R = H)

A mixture of psoralidin (1 g), methanol (100 cc) and conc HCl (28 cc) was refluxed for 2 hr and allowed to stand overnight at room temp. The crystalline material that separated out gave on crystallization from methanol isopsoralidin (VI, R = H; 0·49 g), m.p. 284–287°. The mixed m.p. with psoralidin was depressed. It showed violet fluorescence in dil ethanolic solution. (Found: C, 71·78; H, 5·18. $C_{20}H_{16}O_5$ requires: C, 71·42; H, 4·80%).

U.V. λ_{max} 209 (ε 44,700), 246 (ε 22,400), 306 (ε 8200) and 349 mμ (ε 29,100).

Isopsoralidin monomethyl ether (VI, R = Me)

A mixture of isopsoralidin (0·31 g), acetone (30 cc), anhydrous potassium carbonate (2 g) and dimethyl sulphate (1·8 cc) was refluxed for 5 hr. The crude solid on crystallization from a mixture of acetone and methanol afforded isopsoralidin methyl ether (VI, R = Me; 0·18 g), m.p. 172–174° and 197–200°. (Found: C, 71·67; H, 5·17. OMe, 9·12. $C_{21}H_{18}O_5$ requires: C, 71·99; H, 5·18. OMe (one), 8·86%).

U.V. λ_{max} 211 (ε 42,100), 244 (ε 22,200), 306 (ε 9200) and 346 mμ (ε 30,800).

Dihydropsoralidin (V, R = H)

A mixture of psoralidin (1·2 g), ethyl acetate (400 cc) and 10% palladium on charcoal catalyst (0·5 g) was stirred in an atmosphere of hydrogen. One mole of hydrogen was absorbed in 15 min

[17] The paper chromatography was run[5] on Whatman No. 1 filter paper using ethanol : water (3 : 1) as the developing solvent. The spot was detected by the blue-violet fluorescence in ultra-violet light. D. P. Chakraborty and P. K. Bose, *J. Ind. Chem. Soc.* 33, 905 (1956).

and after that there was no appreciable uptake of hydrogen. The hydrogenated product on crystallization from ethyl acetate afforded dihydropsoralidin (V, R = H; 0·85 g), m.p. 274–276°. (Found: C, 71·39; H, 5·09. $C_{20}H_{18}O_5$ requires: C, 70·99; H, 5·36%)
U.V. λ_{max} 210 (ε 39,000), 244 (ε 22,000), 305 (ε 7500) and 345 mμ (ε 27,700).

Dihydropsoralidin dimethyl ether (V, R = Me)

(a) A mixture of psoralidin dimethyl ether (0·8 g), ethyl acetate (300 cc) and 10% palladium on charcoal catalyst (0·2 g) was stirred in an atmosphere of hydrogen. One mole of hydrogen was absorbed in 20 min. The hydrogenated product on crystallization from acetone afforded dihydropsoralidin dimethyl ether (V, R = Me; 0·65 g), m.p. 193–195°. (Found: C, 71·62; H, 6·16. $C_{22}H_{22}O_5$ requires: C, 72·11; H, 6·05%).
U.V. λ_{max} 209 (ε 39,100), 243 (ε, 21,600), 304 (ε 7700) and 344 mμ (ε 26,500).

(b) A mixture of dihydropsoralidin (0·25 g), anhydrous potassium carbonate (2 g), dimethyl sulphate (1·75 cc) and acetone (30 cc) was refluxed for 5 hr. Dihydropsoralidin dimethyl ether (0·2 g) thus obtained melted at 192–195° and was identical with the material reported above.

Alkali fusion of psoralidin

Isolation of resorcinol and β-resorcylic acid. An intimate mixture of psoralidin (1 g) and potassium hydroxide (5 g) was heated to 300° (bath). The temp was then lowered to 250° (bath) and kept at that temp for 1 hr. The fused mass was dissolved in water, acidified and extracted with ether. The ether solution was washed with Na_2CO_3 solution, then with water, dried (Na_2SO_4) and evaporated to furnish a brown gummy residue (0·4 g), which on evaporative distillation at 130–140°/2 mm gave resorcinol, m.p. 100–104° identical with an authentic specimen (mixed m.p. and infra-red). (Found: C, 65·36; H, 5·29. Calc. for $C_6H_6O_2$: C, 65·44; H, 5·49%).

From the carbonate soluble fraction was obtained, on acidification and extraction with ether, a gummy acid (0·29 g), which on esterification with ethereal diazomethane followed by sublimation at 110–115°/0·3 mm yielded methyl β-resorcylate, m.p. 115–117°, identical (mixed m.p. and infra-red) with an authentic specimen. (Found: C, 57·23; H, 4·77. Calc. for $C_8H_8O_4$: C, 57·14; H, 4·80%).

Chromium trioxide oxidation of psoralidin dimethyl ether

Isolation of acetone. A mixture of psoralidin dimethyl ether (0·36 g), chromium trioxide (0·85 g), glacial acetic acid (15 cc) and water (5 cc) was allowed to stand at room temp for 70 hr. The reaction mixture was diluted with water and steam distilled. To the distillate 2,4-dinitrophenyl hydrazine reagent[18] was added when an immediate precipitate was obtained. The precipitate on crystallization from methanol yielded 2,4-dinitrophenyl hydrazone of acetone, m.p. 126°, identical with an authentic specimen (mixed m.p.). (Found: C, 45·14; H, 4·40. Calc. for $C_9H_{10}O_4N_4$: C, 45·38; H, 4·23%).

Nitric acid oxidation of dihydropsoralidin

Isolation of isocaproic acid. Nitric acid (*d* 1·42, 11·7 cc) was cautiously added with cooling to dihydropsoralidin (0·87 g) and the mixture was kept at room temp for 66 hr, then diluted with water (330 cc) and again kept for 48 hr. Finally the reaction mixture was further diluted with water (780 cc) and steam-distilled. The first 500 cc of the distillate was cooled, saturated with NaCl and extracted with ether. The ether solution on evaporation gave an oil (56 mg) with characteristic odour of isocaproic acid. The presence of isocaproic acid in the oil was established by paper chromatography.[5,19] The solvent system[20] used was ethanol (95%): ammonia (sp. gr. 0·99): water (80 : 5 : 15). Whatman No. 1 filter paper was used. The chromatogram was sprayed with bromocresol green (pH 7), when yellow spot (R_f 0·58) was detected. This was identified as isocaproic acid by co-chromatogram with a pure specimen of isocaproic acid.

Methyl psoralidinate trimethyl ether (VII)

Psoralidin dimethyl ether (100 mg) was dissolved in 10% methanolic KOH solution (20 cc) by heating. The warm solution was alternately treated several times with dimethyl sulphate and aqueous

[18] A. L. Wilds in *Organic Reactions* (Edited by Roger Adams) Vol. II, p. 200. John Wiley, New York (1944).
[19] D. P. Burma and B. Banerjee, *J. Ind. Chem. Soc.* **28**, 135 (1951).
[20] A G. Long, J. R. Quayle and R. J. Stedman, *J. Chem. Soc.* 2197 (1951).

10% KOH solution, in such a way that the final reaction mixture remained slightly alkaline. Extraction with ether in the usual manner gave a crude solid (60 mg), m.p. 102–105°, which on crystallization from methanol furnished the ester (VII), m.p. 114–115°. It showed bluish-violet fluorescence in dil ethanol. (Found: C, 70·24; H, 6·28. $C_{24}H_{26}O_6$ requires: C, 70·23; H, 6·39%).
U.V. λ_{max} 206 (ε 40,300), 229 (ε 30,400) and 325 mμ (ε 16,500).
I.R. Peaks at 1705 (conjugated ester), 1620 (conjugated C=C) and 1598 and 1500 cm^{-1} (aromatic nucleus).

Dihydropsoralidinic acid trimethyl ether (VIII, R = H)

Similarly dihydropsoralidin dimethyl ether (0·9 g) in 10% methanolic KOH solution (125 cc) on alternate treatment with dimethyl sulphate and 10% aqueous KOH solution yielded the dihydro-ester (VIII, R = Me; 0·58 g) as an oil, λ_{max} 207 (*E* 32,600), 227 (*E* 29,700) and 325 mμ (*E* 15,500), which resisted all attempts at crystallization.

The oil (0·5 g) was refluxed for 6 hr with 10% methanolic NaOH solution (5 cc), then cooled, diluted with water and acidified with cold dil HCl, when a crystalline solid was obtained. On crystallization from methanol the solid gave the acid (VIII, R = H; 0·42 g), m.p. 197–198°d. (Found: C, 68·99; H, 6·53. $C_{23}H_{26}O_6$ requires: C, 69·33; H, 6·58%).
U.V. λ_{max} 212 (ε 35,200) and 319 mμ (ε 20,000).
I.R. Peaks at 1678 (conjugated carboxyl), 1620 (conjugated C=C) and 1582 and 1498 cm^{-1} (aromatic nucleus).

2-(2,4-*Dimethoxy*-5-(3-*methylbutyl*)-*phenyl*)-6-*methoxy benzofuran* (IX)

An intimate mixture of dihydropsoralidinic acid trimethyl ether (1·2 g) and glass powder (0·2 g) was heated at 210° (bath) for 2 hr. The reaction mixture on sublimation at 190°/0·2 mm furnished the benzofuran (IX; 0·97 g), m.p. 80–83°. On crystallization from methanol, the analytical sample melted at 84–86°. (Found: C, 74·33; H, 7·02. $C_{22}H_{26}O_4$ requires: C, 74·55; H, 7·39%).
U.V. λ_{max} 212 (ε 34,000), 281 (ε 13,000), 223 (ε 37,300) and 338 mμ (ε 36,100).
I.R. Peaks at 1620 (conjugated C=C), 1582 and 1496 (aromatic nucleus), 1264 (aromatic C—O), 1110 (aromatic ether) and 1035 cm^{-1} (OMe).

Osmium tetroxide oxidation of the benzofuran (IX)

Isolation of the benzoin (XI). A solution of osmium tetroxide (0·69 g) in benzene (3·5 cc) was added to a solution of the benzofuran (IX, 1·03 g) in benzene (3 cc) and pyridine (8 drops) and the reaction mixture was allowed to stand at room temp for 5 days. The black osmate derivative was decomposed by stirring for 20 hr at room temp with ethanol (27 cc) and saturated aqueous Na_2SO_3 solution (27 cc). The mixture was then diluted with water (200 cc) and extracted with ether. The ether solution on evaporation furnished a gummy residue (0·89 g), which on crystallization from methanol gave the benzoin (XI, 0·38 g), m.p. 104–108°. On recrystallization from methanol, the analytical sample melted at 113–115°. It gave a blue-violet colour with alcoholic ferric chloride solution. (Found: C, 68·37; H, 6·96. $C_{22}H_{28}O_6$ requires: C, 68·02; H, 7·27%).
U.V. λ_{max} 212 (ε 35,400), 230 (ε 24,000), 279 (ε 21,300) and 326 mμ (ε 18,000).
I.R. Peaks at 3500 (hydroxyl), 1635 (conjugated ketone) and 1605, 1575 and 1498 cm^{-1} (aromatic nucleus).

Periodate oxidation of the benzoin (XI)

Isolation of 2-*hydroxy*-4-*methoxy-benzaldehyde and* 2,4-*dimethoxy*-5-(3-*methylbutyl*)-*benzoic acid* (XII). A solution of the benzoin (XI, 0·79 g), sodium metaperiodate (0·87 g), methanol (50 cc) and water (5 cc) was allowed to stand at room temp for 24 hr. The reaction mixture was diluted with water and extracted with ether. The ether solution was washed with cold 5% aqueous Na_2CO_3, then with water, dried (Na_2SO_4) and evaporated to give trace of an oil, λ_{max} 230, 279 and 315 mμ, which was converted to its 2,4-dinitrophenyl hydrazone and was found to be identical with the 2,4-dinitrophenyl hydrazone of 2-hydroxy-4-methoxy-benzaldehyde (R_f 0·62) by paper chromatography.[21]

The above aqueous carbonate solution on acidification with dil HCl yielded a crystalline acid (60 mg), m.p. 80–84°, which on crystallization from cyclohexane gave the acid (XII), m.p. 90–91°,

[21] The developing solvent was ethanol : formamide : water (8 : 1 : 1).

identical (mixed m.p. and infra-red) with an authentic specimen described below. (Found: C, 66·37; H, 7·80. $C_{14}H_{20}O_4$ requires: C, 66·64; H, 7·99%).
I.R. Peaks at 1720 (conjugated carbonyl), 1610, 1580 and 1500 (aromatic nucleus), 1270 and 1110 (aromatic ether) and 1027 cm^{-1} (OMe).

2,4-*Dinitrophenyl hydrazone of* 2-*hydroxy*-4-*methoxy-benzaldehyde* (*authentic*)

2-Hydroxy-4-methoxy-benzaldehyde,[22] m.p. 40–41° was converted in the usual manner to its 2,4-dinitrophenyl hydrazone, which after crystallization from benzene melted at 264° (Reported[23] m.p. 256°). (Found: C, 50·58; H, 3·79. Calc. for $C_{14}H_{12}O_6N_4$: C, 50·60; H, 3·64%).

Synthesis of 2,4-*dimethoxy*-5-(3-*methylbutyl*)-*benzoic acid* (XII)

Methyl 2,4-*dihydroxy*-5-*isovaleryl benzoate* (XIII, R = H). To a cold solution of methyl β-resorcylate (3·8 g) in nitrobenzene (45 cc) was added powdered aluminium chloride (6·6 g) with stirring. The mixture was stirred until the entire aluminium chloride dissolved to form a light brown viscous mass. To this viscous solution was added freshly distilled isovaleryl chloride (3·1 g) in nitrobenzene (60 cc) and the solution stirred for 10 hr at 40–45°. Finally the reaction mixture was poured into ice and conc HCl and extracted with ether. The residue after the removal of ether gave crystals (4·6 g), m.p. 65–72° on cooling. The crystals on sublimation followed by crystallization from aqueous methanol gave the ester (XIII, R = H), m.p. 70–72° (Reported[15] m.p. 74°).
U.V. λ_{max} 244 (ε 45,800) and 313 mμ (ε 5900)

2,4-*dinitrophenyl hydrazone* of the above keto-ester was prepared in 85% yield in the usual manner. On crystallization from methanol it melted at 202–203° (Found: C, 52·50; H, 4·64. $C_{19}H_{20}O_8N_4$ requires: C, 52·78; H, 4·66%)

Methyl 2,4-*dimethoxy*-5-*isovaleryl*-*benzoate* (XIII, R = Me)

A mixture of the keto-ester (XIII, R = H, 0·6 g), anhydrous potassium carbonate (7 g), acetone (30 cc) and dimethyl sulphate (7 cc) was refluxed for 6 hr. On usual working up a crystalline solid (0·51 g), m.p. 120–125° was obtained. The solid, which showed negative ferric chloride test, on crystallization from methanol yielded the keto-ester (XIII, R = Me), m.p. 129–130°. (Found: C, 64·07; H, 7·28. $C_{15}H_{20}O_5$ requires: C, 64·27; H, 7·19%).
U.V. λ_{max} 239 (ε 29,600), 272 (ε 13,200) and 299 mμ (ε 5400).

2,4-*Dimethoxy*-5-(3-*methylbutyl*)-*benzoic acid* (XII)

A mixture of the keto-ester (XIII, R = Me, 0·36 g), glacial acetic acid (20 cc), 10% palladium on charcoal catalyst (0·1 g) and perchloric acid (0·1 cc) was stirred in an atmosphere of hydrogen. Two mole equivalent of hydrogen was absorbed in 15 min, then the hydrogenated product was worked up in the usual manner to yield a gum (0·35 g), which was saponified by refluxing for 2 hr with 5% methanolic KOH solution (5 cc). The reaction mixture on dilution followed by acidification yielded a crystalline acid (0·28 g), m.p. 84–85°, which on crystallization from cyclohexane furnished the acid (XII), m.p. 90–91°, identical (mixed m.p. and infra-red) with the acid (XII) obtained from psoralidin reported above. (Found: C, 66·59; H, 8·00. $C_{14}H_{20}O_4$ requires: C, 66·64; H, 7·99%).

Acknowledgements—We are highly indebted to Dr. George R. Petit of the University of Maine, Orono, Maine, U.S.A., to Dr. E. J. Eisenbraun, Stanford University, Stanford, California, U.S.A. and to Dr. Tapan K. Mukerji for the infra-red spectra of our compounds. We are also indebted to Dr. (Mrs.) A. Chatterjee, University College of Science, Calcutta, for the gift of osmium tetroxide and to Mr. P. Bagchi, Research Director, E. I. P. W. Ltd. for encouragement.

[22] H. A. Offe and H. Jatzkewitz, *Chem. Ber.* **80**, 469 (1947).
[23] F. Weygand and R. Mitgan, *Chem. Ber.* **88**, 301 (1955).