# 1156. *A Partial Synthesis of (±)-Pisatin: Some Remarks on the Structure and Reactions of Pterocarpin.*

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Controlled action of acid on pterocarpin (I; R = H) or homopterocarpin (II, R = H) produces the isoflavenes (V; R = H) or (VI; R = H), respectively. Hydrogenation of (V; R = Me) gives the flavan (IV; R = Me) with the properties reported for the synthetic compound, thus further supporting formula (I; R = H) for pterocarpin. Oxidation of the isoflavenes (V; R = Ac) and (VI; R = Ac) with osmium tetroxide, followed by the action of alkali, leads to (±)-pisatin (I; R = OH) and the analogue (II; R = OH). Reaction of pterocarpin and homopterocarpin with potassamide in liquid ammonia leads to benzofuran derivatives of type (X).

The phytoalexins are very important plant protective agents, biosynthesised in response to fungal attack.[1] Those of known structure include the terpene ipomeamarone,[2] and the phenolic derivatives orchinol,[3] hircinol,[4] an isocoumarin from carrots,[5] trifolirhizin,[6] phaseollin[7] and pisatin[8] (I; R = OH). The last three are related isoflavan derivatives, and other known natural compounds of this class may also be protective agents; homopterocarpin (II; R = H) from the heartwoods of *Pterocarpus* species[9] appears to be as active a plant anti-fungal agent as pisatin.[10] In view of their biological interest and the difficulty of obtaining notable amounts from the natural sources, partial or total syntheses of the phytoalexins and analogues is desirable. We report a partial synthesis of (±)-pisatin (I; R = OH) from the readily available[9] pterocarpin (I; R = H) and of the analogue (II; R = OH) from homopterocarpin[9] (II; R = H).

When this work was begun the structure assigned to pisatin was based[11] on an erroneous formula (III) for pterocarpin. The structure of the latter was revised to (I; R = H) initially on the basis of n.m.r. spectra[12] and later[13] by a comparison of synthetic (±)-dihydropterocarpin methyl ether (IV; R = Me), m. p. 111—112°, with the (−)-compound (IV; R = Me), m.p. 116—117°, obtained by catalytic hydrogenolysis of (−)-pterocarpin followed by methylation. The comparison, by means of infrared spectra in chloroform solution, although probably accurate, would have been more convincing if a similar comparison had not originally[14] led to structure (III). Consequently, a comparison seemed desirable between the properties of the authentic synthetic (±)-ether (IV; R = Me) and the same compound from (−)-pterocarpin.

The action of acid on pterocarpin should initially produce compound (V; R = H) by fission of the benzyl ether linkage, and this is a key compound for conversion into (±)-compound (IV; R = Me) and into (±)-pisatin. The previous literature indicates the instability to acid of pterocarpin and homopterocarpin but only red resins were reported to result. By carefully

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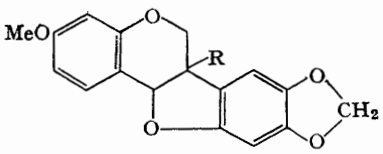
controlled reaction the isoflavenes (V; R = H) and (VI; R = H) were obtained. The structure of compound (VI; R = H) is supported by its ultraviolet absorption ($\lambda_{max.}$ 242, 328 mμ; log ε 3·94, 4·02) which differs from that of pterocarpin ($\lambda_{max.}$ 286, 310 mμ) and is similar to that of 4',7-dimethoxyisoflav-3-ene ($\lambda_{max.}$ 250, 335 mμ; log ε 4·17, 4·39); it is also weakly phenolic. Methylation of compound (V; R = H) gave compound (V; R = Me), which on hydrogenation produced the desired (±)-compound (IV; R = Me), m. p. 110—111°, $\lambda_{max.}^{*}$ 228 (sh), 290, 300 mμ, in accord with the properties recorded for synthetic (±)-compound (IV; R = Me).[13] The m. p. differs widely from that of the isomeric synthetic compound



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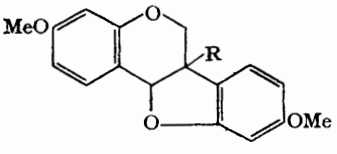

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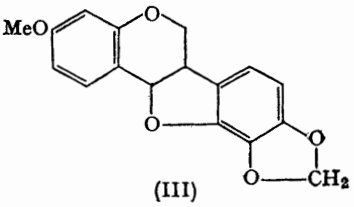

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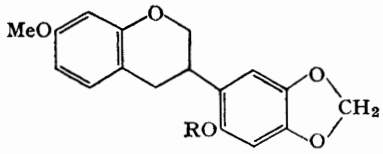

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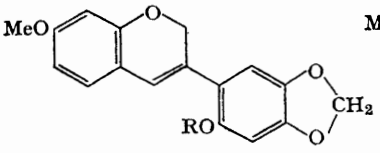

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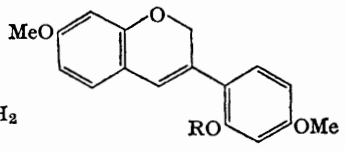

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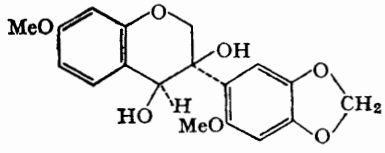

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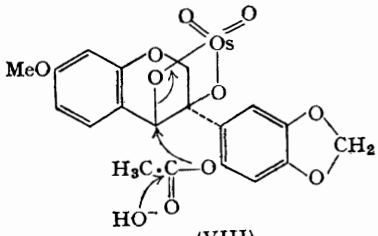

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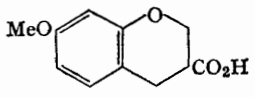

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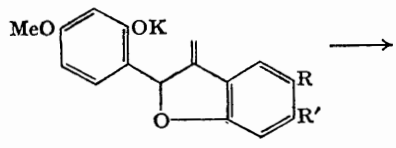

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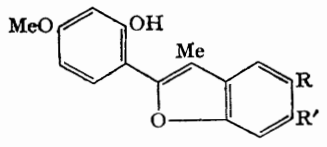

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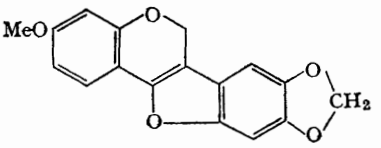

(XI)

(86°)[14] on which structure (III) was based. No direct comparison could be made, but accumulation of evidence leaves no reasonable doubt that structure (I; R = H) correctly represents pterocarpin.

Formulation of (+)-pisatin as (I; R = OH) seems well founded,[8] chiefly on the basis of spectral comparisons with pterocarpin. Its synthesis from compound (V; R = H) would necessarily involve oxidation of the double bond, but, in view of the known extreme instability of pisatin to acid, avoidance of acidic conditions for production of the ether ring seemed highly desirable. Attempts to oxidise compound (V; R = Me) with per-acids led to red gums, but it reacted readily with osmium tetroxide to give finally the expected glycol (VII). The ester (V; R = Me) similarly reacted to produce the osmate ester (VIII). In order to produce the ether ring under alkaline conditions this ester was reacted with sodium carbonate in the hope of achieving the displacement reaction shown. In fact, the product

of the reaction, m. p. 188—190°, had the properties expected for (±)-pisatin. The infrared spectrum in carbon tetrachloride was identical with that of (+)-pisatin, and the ultraviolet spectra were superimposable. The last fact seems significant since, despite the similarity of the absorption of compound (VII), the curves differ in detail. The action of acid gave anhydropisatin (XI) identical with the authentic compound and the (±)-compound was found to have the full antifungal activity[10] of the natural (+)-isomer.

A similar series of reactions on (−)-homopterocarpin (II; R = H) gave rise to (II; R = OH) which is also highly antifungal.[10] From the assumed mechanism shown the ring junctions resulting in both cases should be *cis*.

The nucleus of the pterocarpin series is interesting in containing two phenolic ether rings on different environments. Ether fission with acid occurs at the benzyl-ether group as noted. Base-catalysed fission by β-elimination should also be possible by initial removal of the proton R in (I; R = H), forming an intermediate benzylic anion, reaction being consummated by elimination of one or other of the ethereal oxygens as an anion. The action of potassamide in liquid ammonia on homopterocarpin gave a crystalline phenolic product, $C_{17}H_{16}O_4$ (X; RR′ = $OCH_2O$), $\lambda_{max.}$ 271, 311 mμ, log ε 4·12, 4·17, which is similar in absorption to 5,6-dimethoxy-2-(2,4,6-trimethoxyphenyl)benzofuran; $\lambda_{max.}$ 275, 310 mμ, log ε 4·15, 4·35. An analogous compound, $C_{17}H_{14}O_5$ (X; R = H, R′ = OMe), was obtained from pterocarpin, and Kuhn–Roth oxidation gave 85% of one mole of acetic acid. Ozonolysis of compound (X; R = H, R′ = OMe) derived from homopterocarpin resulted in production of 2-hydroxy-4-methoxyacetophenone, thus confirming the assigned structure. These results indicate initial fission to substances of type (IX) and a mechanistically acceptable migration of the double bond to give the stable benzofuran structure of type (X). If the ring junction is the stable *cis*-form, the molecule can readily take up a conformation permitting *trans*-elimination in the appropriate direction.

Although the identical sign and similarity of optical rotations of pterocarpin and homopterocarpin make identity of their absolute configurations virtually certain, we have confirmed this by oxidation of (−)-dihydropterocarpin (IV) and (−)-dihydrohomopterocarpin to the same acid (XII), $[\alpha]_D$ +29·8°. This acid has been obtained previously[14] but the rotation had not been measured.

From the opposite signs of rotation, (+)-pisatin and (−)-pterocarpin probably have opposite absolute configurations,[11] that of the pterocarpin being determined by that of the flavanone from which it is probably derived biogenetically. The configuration of the pisatin may therefore be established during a final oxidation stage, and a flav-3-ene of the type used as a synthetic intermediate may also be a biosynthetic intermediate.

A preliminary account of some of this work has been published.[15]

## Experimental

*2′-Hydroxy-4′,7-dimethoxyisoflav-3-ene.*—(−)-Homopterocarpin (500 mg.) in ethanol (12 c.c.) and 10N-hydrochloric acid (0·25 c.c.) was refluxed for 10 min., poured into water (150 c.c.) and extracted with ether. Removal of the solvent left a residue which rapidly crystallised. The *2′-hydroxy-4′,7-dimethoxyisoflav-3-ene* (340 mg.) crystallised from benzene as colourless crystals which readily turned pink, m. p. 122—124° (Found: C, 71·7; H, 5·65. $C_{17}H_{16}O_4$ requires C, 71·8; H, 5·67%); $\lambda_{max.}$ 242 and 328 mμ (log ε 3·94, 4·02). Acetylation with acetic anhydride and pyridine in the usual manner gave *2′-acetyl-4′,7-dimethoxyisoflav-3-ene*, crystallised from chloroform–ethanol as plates, m. p. 132—134° (Found: C, 70·3; H, 5·6. $C_{19}H_{18}O_5$ requires C, 69·9; H, 5·5%); $\lambda_{max.}$ 242 and 321 mμ (log ε 3·91, 4·03).

*3-Hydroxy-4′,7-dimethoxychromanocoumaran.*—The above acetyl derivative (200 mg.) in pure tetrahydrofuran (2 c.c.) and pyridine (0·5 c.c.) was added to osmium tetroxide (80 mg.) in ether (5 c.c.) at 0°. After being left overnight the mixture was diluted with dry ether and the precipitated osmate ester removed by filtration. It was dissolved in chloroform (15 c.c.) and shaken with 0·1N-sodium carbonate solution (15 c.c.) containing mannitol (0·5 g.). The chloroform layer was

[15] C. W. L. Bevan, A. J. Birch, B. Moore, and S. K. Mukerjee, *Tetrahedron Letters*, 1962, 673.

extracted with several successive amounts of sodium carbonate solution and then run through a short column of activated charcoal. The gum (120 mg.) obtained by evaporation did not crystallise, but had an ultraviolet spectrum virtually identical with that of homopterocarpin. The gum was dissolved in ethanol (3 c.c.) and water (5 c.c.) containing ammonium chloride (0·5 g.). Dilution with water and re-extraction gave a gum which crystallised from ether–light petroleum as colourless prisms (55 mg.). The *3-hydroxy-4′,7-dimethoxychromanocoumaran* had m. p. 118—120° (Found: C, 68·4; H, 5·5. $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·3%); $\nu_{max.}$ 3640, 1620, 1600, and 1500 cm.$^{-1}$; $\lambda_{max.}$ 285 and 301 (log ε 3·93, 2·33). The crude compound from decomposition of the osmate ester (90 mg.) in ethanol (2 c.c.) and 0·1N-hydrochloric acid (5 c.c.), left for 12 hr., gave a crystalline deposit, recrystallised from aqueous ethanol. The *4′,7-dimethoxychromenocoumaran* was obtained as pale yellow plates (41 mg.), m. p. 100—102° (Found: C, 72·1; H, 5·3. $C_{17}H_{14}O_4$ requires C, 72·3; H, 5·0%); $\lambda_{max.}$ 335 and 350 mμ [log ε 4·45, 4·39 (ethanol)].

*Reduction of Pterocarpin and Homopterocarpin.*—(−)-Homopterocarpin (14 g.) in a mixture of tetrahydrofuran (25 c.c.) and ethanol (75 c.c.) was added to liquid ammonia (500 c.c.) followed by sodium (7 g.) in portions over 20 min. After evaporation of most of the ammonia, water (500 c.c.) and 10N-hydrochloric acid (25 c.c.) were added. The (−)-dihydrohomopterocarpin (13·1 g.), crystallised from ethanol, had m. p. 152—154°, $\lambda_{max.}$ 285 mμ (log ε 3·85). (−)-Dihydropterocarpin, m. p. 144—146°, $\lambda_{max.}$ 230 and 301 mμ [log ε 3·85, 3·81 (ethanol)], was obtained similarly; the methyl ether had m. p. 114°.

*7-Methoxychroman-3-carboxylic Acid.*—(−)-Dihydrohomopterocarpin (1·07 g.) was dissolved in acetone, and potassium permanganate (3·75 g.) in water (75 c.c.) added over 30 min. After 14 hr. sulphur dioxide was used to dissolve the precipitate, the solution concentrated, acidified, and the product extracted with ether. The acid was removed from the ether by extraction with sodium hydrogen carbonate solution and crystallised from aqueous ethanol. The (+)-*7-methoxychroman-3-carboxylic acid* had m. p. 146—149° (Found: C, 63·3; H, 5·6. $C_{11}H_{12}O_4$ requires C, 63·5; H, 5·8%), $\lambda_{max.}$ 284 and 345 mμ (log ε 3·5, 2·75), $[\alpha]_D^{23°}$ + 29·8° (ethanol, *c* 1·4%). (−)-Dihydropterocarpin gave the same product with almost identical rotation.

*2′-Hydroxy-7-methoxy-4′,5′-methylenedioxyisoflav-3-ene.*—To (−)-pterocarpin (2·51 g.) in refluxing ethanol (140 c.c.) was added a mixture of ethanol (7 c.c.) and 10N-hydrochloric acid (2·75 c.c.); refluxing was continued for 10 min. After dilution with water (15 c.c.) and cooling, unchanged pterocarpin (925 mg.) crystallised and was removed. After dilution with a large volume of water the filtrate slowly deposited the crude isoflavene (1·25 g.), m. p. 110—118°. Two crystallisations from ether–light petroleum gave *2′-hydroxy-7-methoxy-4′,5′-methylenedioxyisoflav-3-ene* (1·05 g.) as pale yellow plates, m. p. 124—126° (Found: C, 68·2; H, 4·7. $C_{17}H_{14}O_5$ requires C, 68·5; H, 4·7%); $\nu_{max.}$ 3655, 3580, 1612, and 940 cm.$^{-1}$; $\lambda_{max.}$ 340 mμ (log ε 4·34).

Hydrogenation in glacial acetic acid with palladium–charcoal gave (±)-2′-hydroxy-7-methoxy-4′,5′-methylenedioxyisoflavan, m. p. 176—178°, from ethanol. Its ultraviolet and infrared spectra were completely identical with those of the (−)-isoflavan, m. p. 146°, obtained from (−)-pterocarpin by reduction.

The above isoflavene was acetylated with acetic anhydride and pyridine to *2′-acetoxy-7-methoxy-4′,5′-methylenedioxyisoflav-3-ene*, m. p. 150—152° (Found: C, 67·0; H, 4·75. $C_{19}H_{16}O_6$ requires C, 67·1; H, 4·8%); $\nu_{max.}$ 1710, 1610, 1570, and 940 cm.$^{-1}$. Methylation of the isoflavene with methyl sulphate and potassium carbonate in acetone gave *2′,7-dimethoxy-4′,5′-methylenedioxyisoflav-3-ene*, which formed a hydrate, m. p. 97—98° from aqueous ethanol, converted by drying *in vacuo* into the anhydrous form, m. p. 110—111° (Found: C, 69·6; H, 4·95. $C_{18}H_{16}O_5$ requires C, 69·2; H, 5·1%); $\nu_{max.}$ 1620, 1045, and 940 cm.$^{-1}$. Oxidation of the latter with osmium tetroxide in pyridine as described above, and decomposition of the osmate ester with aqueous potassium hydroxide (0·1N) containing mannitol, gave *3,4-dihydroxy-2′,7-dimethoxy-4′,5′-methylenedioxyisoflavan*, m. p. 195—197° (Found: C, 51·9; H, 5·45. $C_{18}H_{18}O_7$ requires C, 62·4; H, 5·2%), $\lambda_{max.}$ 290 mμ (log ε 3·85).

(±)-*Pisatin.*—A solution of the above acetoxyisoflavene (100 mg.) in tetrahydrofuran (4 c.c.) and pyridine (0·2 c.c.) reacted slowly with osmium tetroxide (80 mg.) in ether (2 c.c.) at 0°. After 12 hr. the osmate ester was precipitated with pure ether (20 c.c.) and decomposed by shaking it in chloroform (10 c.c.) with 0·1N-sodium carbonate (30 c.c.) containing mannitol (0·5 g.) for 3 hr. The chloroform layer was decolourised by shaking it with a little charcoal and concentrated under reduced pressure. Addition of light petroleum caused slow decomposition of crude (±)-pisatin (42·5 mg.) which was crystallised from chloroform–light petroleum, m. p. 188—190° (Found: C, 64·9; H, 4·7. Calc. for $C_{17}H_{14}O_6$: C, 64·9; H, 4·5%); $\lambda_{max.}$ 285·5 and 309 mμ [log ε 3·56, 3·94

(ethanol)]; $\nu_{max.}$ 3530, 1620, and 1590 cm.$^{-1}$ (chloroform). The action of acid gave anhydropisatin, m. p. 179—180°, $\lambda_{max.}$ 239 and 257 mμ, unchanged by an authentic specimen.

(±)-2′,7-*Dimethoxy*-4′,5′-*methylenedioxyisoflavan*.—Hydrogenation of 2′,7-dimethoxy-4′,5′-methylenedioxyisoflav-3-ene with a palladium–charcoal catalyst in glacial acetic acid gave the isoflavan compound, m. p. 110—111° (Found: C, 69·0; H, 5·9. Calc. for $C_{18}H_{18}O_5$: C, 68·8; H, 5·7%).

2-(2-*Hydroxy*-4-*methoxyphenyl*)-5-*methoxy*-3-*methylbenzofuran*.—(−)-Hompterocarpin (1 g.) in tetrahydrofuran (10 c.c.) was added to a solution of potassamide [from the metal (1 g.)] in liquid ammonia (150 c.c.). After 10 min., water (300 c.c.) and 10N-hydrochloric acid (3 c.c.) were cautiously added. After ether extraction the 2-(2-*hydroxy*-4-*methoxyphenyl*)-5-*methoxy*-3-*methylbenzofuran* (895 mg.) crystallised from ethanol; it had m. p. 111° (Found: C, 71·7; H, 5·55; *C*–Me, 4·75. $C_{17}H_{16}O_4$ requires C, 71·8; H, 5·7; *C*–Me, 5·3%); $\lambda_{max.}$ 271 and 311 mμ (log ε 4·12, 4·27).

(−)-Pterocarpin, treated as above, gave 2-(2-*hydroxy*-4-*methoxyphenyl*)-3-*methyl*-6,7-*methylenedioxybenzofuran*, m. p. 120—122° (Found: C, 69·0; H, 4·75. $C_{17}H_{14}O_5$ requires C, 68·5; H, 4·7%); $\lambda_{max.}$ 271 and 322 mμ (log ε 4·13, 4·39).

The above benzofuran (270 mg.), m. p. 111°, was ozonised in methanol (20 c.c.) in the standard manner, the ozonide being decomposed by hydrogenation. The product was hydrolysed with 1N-aqueous methanolic sodium hydroxide, acidified, and the ether solution extracted with sodium hydrogen carbonate. Evaporation of the ether left an oil which crystallised from light petroleum. The 2-hydroxy-4-methoxyacetophenone, m. p. 49°, gave a deep-purple colour with ferric chloride and was undepressed in m. p. by an authentic specimen, m. p. 50°. The 2,4-*dinitrophenylhydrazone* formed dark orange-red crystals, m. p. 228—232° (Found: C, 52·1; H, 3·9. $C_{15}H_{14}N_4O_6$ requires C, 52·1; H, 3·9%).

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