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The Synthesis of *d, l*-Homopterocarpin[1)]

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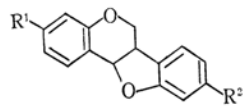
The synthesis of chromanocoumaran (I) ($R^1=R^2=H$), the skeleton of pterocarpinoids, is described. This method, which follows a plausible biogenetic pathway, is then extended to the synthesis of *d, l*-homopterocarpin (I) ($R^1=R^2=OMe$). The synthesis and NMR studies allow us to assign a cis B/C ring junction to the compounds of this class.

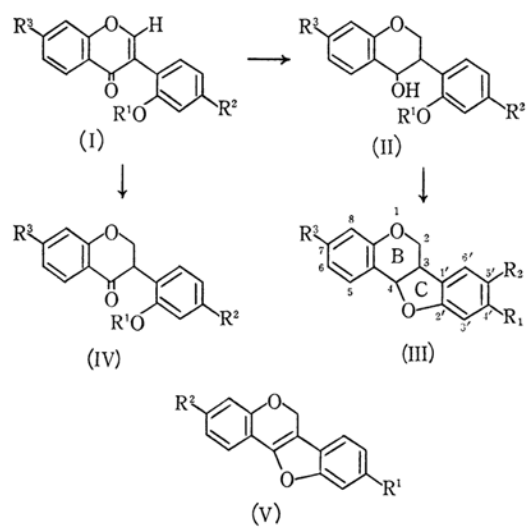


(I)

Pterocarpin and homopterocarpin were first isolated by Cazeneuve in 1874.[2)] The structure of homopterocarpin was elucidated in 1940 by Späth and Schläger[3)] and by Robertson et al.[4)] as III ($R^1=R^3=OMe$, $R^2=H$). The structure of pterocarpin was also elucidated by Robertson et al.[4)] and, more recently, by Bredenberg and Shoolery[5)] spectroscopically, and also by one of the present authors synthetically,[6)] as III ($R^3=OMe$, R^1, $R^2=-O-CH_2-O-$). However, the syntheses of these natural products, even their simple cores, have not been completed. This paper is an account of the syntheses of their skeleton and the racemic homopterocarpin.

In view of an apparent biogenetic link of these naturally-occurring chromanocoumarans to 2'-hydroxyisoflavonoids,[7)] the synthetic sequence was chosen in order to trace a plausible biogenetic path.

In explorative studies, the skeleton III ($R^1=R^2=R^3=H$) of pterocarpin was synthesized for the first time.



(I) (II) (IV) (III) (V)

It was found that the mild acid hydrolysis of liquid 2 : 2'-bismethoxymethoxybenzoin[8)] which had been purified by distillation yielded 2 : 2'-dihydroxybenzoin, together with a second product. This was identified as the corresponding benzil. It showed a doublet carbonyl absorption in its infrared spectrum (1614 cm^{-1} and 1631 cm^{-1}) and an absorption maxima at 256 mμ (ε, 14930) and 330 mμ (ε, 6300) in its ultraviolet spectrum. It was apparent that the original, protected benzoin was contaminated by the corresponding benzil, which could be isolated as crystals from liquid 2 : 2'-bismethoxymethoxybenzoin. This benzil may be produced by autooxidation during distillation, and La Forge's liquid bismethoxymethoxybenzoin could be a mixture of benzoin and the

1) Oxygen Heterocycles. VIII. Read before the 15th Annual Meeting of the Chemical Society of Japan, Tokyo, April, 1962. A brief account of this work has already been published. H. Suginome and T. Iwadare, This Bulletin, **33**, 568 (1960); *Experientia,* **18**, 163 (1962).

2) a) P. Cazeneuve, *Ber.*, **7**, 1798 (1874); P. Cazeneuve, *Bull. Soc. Chim. France.*, **23**, 97 (1875); P. Cazeneuve, and L. Hugouneng, *Compt. Rend.*, **104**, 1722 (1887). b) P. L. Sawhney and T. R. Seshadri, *J. Sci. and Ind. Res.*, **13B**, 5 (1954). c) F. E. King, C. B. Cotterill, D. H. Godson, L. Jurd and T. J. King, *J. Chem. Soc.*, **1953**, 3693. d) A. Akisanya, C. W. L. Bevan and J. Hirst, ibid., **1959**, 2679.

3) E. Späth and J. Schläger, *Ber.*, **73**, 1 (1940).

4) A. McGookin, A. Robertson and W. B. Whalley, *J. Chem. Soc.*, **1940**, 787.

5) J. B. Bredenberg and J. N. Shoolery, *Tetrahedron Letters,* **1961**, 285.

6) H. Suginome, *Experientia,* **18**, 161 (1962); and preceding paper.

7) H. Suginome, *J. Org. Chem.*, **24**, 1655 (1959); H. Suginome, *Tetrahedron Letters,* **1960**, 16.

8) F. B. LaForge, *J. Am. Chem. Soc.*, **55**, 3040 (1933).

corresponding benzil. The mixture of 2 : 2′-dihydroxybenzoin and benzil thus obtained was reduced with zinc and sodium hydroxide to yield 2 : 2′-dihydroxydesoxybenzoin (m. p. 102—103°C), together with a small amount of 2′-(*O*-hydroxyphenyl)-coumarone. This desoxybenzoin was then transformed to the corresponding 2′-hydroxyisoflavone with sodium and ethyl formate.[9] No isomeric 3-benzoylcoumarone and intermediary 2-hydroxyisoflavanone could be isolated. It has already been suggested by Whalley[10] that a 2′-methoxy subsituent is necessary to isolate an intermediary 2-hydroxyisoflavanone in the reaction of desoxybenzoin with sodium and alkyl formates, since a weak hydrogen bonding between the 2-hydroxyl group and the 2′-methoxy group will be a major contributing factor to the stability of the 2-hydroxyisoflavanone system. In the present investigation, obviously the hydrogen bond between the 2′-hydroxyl group and the carbonyl group is stronger than that between the 2′ and 2-hydroxyl functions. This must be the reason for the failure to isolate an intermediate 2-hydroxyisoflavanone. The 2′-hydroxyisoflavone thus obtained was reduced to the corresponding isoflavanone in the presence of Adams' platinum catalyst. This isoflavanone was very easily converted to chromenocoumarone (V) ($R^1=R^2=H$) (m. p. 87—89°C) with 50% acetic acid, thus confirming the conversion of sophorol to anhydrosophorol.[7] The ultraviolet spectrum of chromenocumarone is shown in Fig. 1. The tetrasubstituted double bond in chromenocoumarone (V) ($R^1=R^2=H$) resists catalytic hydrogenation in the presence of the platinum catalyst. 2′-Hydroxyisoflavone was reduced to a liquid stereoisomeric mixture of 2′-hydroxyisoflavan-4-ol with either sodium borohydride[11] or lithium aluminum hydride. In the case of dehydrorotenone, reduction with lithium aluminum hydride leads to the corresponding isoflavan-4-ol, whereas reduction with sodium borohydride results in the formation of the corresponding isoflav-2-en-4-ol.[11] It is of interest to note that, in the present case, reduction with both these metal hydrides resulted in the isolation of the same product, which is probably due to the 1, 4-addition of hydride reagents to the γ-pyrone system followed by further reduction. This crude isoflavan-4-ol was successfully converted into the pterocarpin ring system. III ($R^1=R^2=R^3=H$) in a 70% yield by mild treatment with 50% acetic acid. No appreciable formation of isoflav-(3)-ene was observed.

The NMR spectrum (Fig. 2) in deuteriochloroform of the synthetic chromanocoumaran shows 8 aromatic protons as the multiplet ranging $\tau=2.34$ to $\tau=3.18$. The doublet centering at $\tau=4.47$, $J=5.7$ c. p. s. (1 proton) is assigned to a proton on position 4, which is coupled only to a proton on the position 3. The Karplus equation[12] has

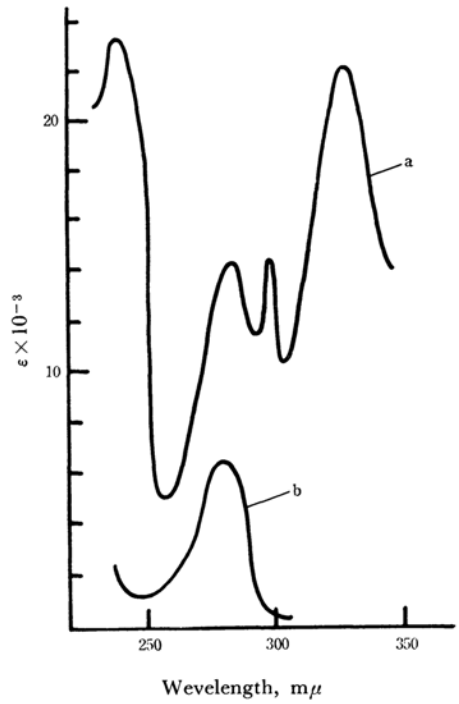


Fig. 1. UV spectra.
a, Chromanocoumarone
b, Chromanocoumaran

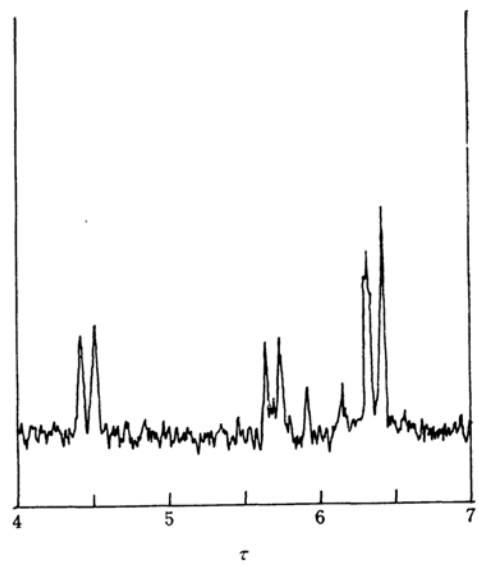


Fig. 2. NMR spectrum of chromanocoumaran.

9) W. H. Perkin and R. Robinson, *J. Chem. Soc.*, **1908**, 489.
10) W. B. Whalley, *J. Am. Chem. Soc.*, **75**, 1059 (1953).
11) M. Miyano and M. Matsui, *Chem. Ber.*, **91**, 2044 (1958).
12) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); R. J. Abraham and K. A. MacLauchlan, *Mol. Phy.*, **5**, 513 (1962); R. J. Abraham and J. S. E. Holker, *J. Chem. Soc.*, **1963**, 806.

been shown experimentally to apply to a wide variety of compounds.

The equation gives $\phi=33°$ for the dihedral angle $-HC^3-C^4H-$. The model inspection obviously favored a B/C ring junction of cis for chromanocoumaran. Although the calculated angle seems to give a higher value than that to be expected from the model, the deviation is perhaps attributable to the electronegativity[13] of the substituent adjacent to the coupling protons. The two hydrogens on the position 2 which constitute the AB part of the ABX system appeared as the triplet centered at $\tau=6.28$. A proton on the position 3 gives rise to the multiplet ranging from $\tau=5.65$ to $\tau=5.92$.

In view of the above described results, the same sequence of reaction was applied to the 2′: 4′: 7-trihydroxyisoflavone (I) ($R^1=H$, $R^2=R^3=OH$) series. The starting material, 2′: 4′: 7-trimethoxyisoflavone, had been synthesized by Späth and Schläger[3] by the reaction of 2-hydroxy-2′ : 4′-trimethoxydesoxybenzoin with methylformate in the presence of sodium. Although they did not isolate any intermediary 2-hydroxyisoflavanone from this reaction, one repetition of this work by using ethylformate led to the isolation of 2-hydroxy-7 : 2′ : 4′-trimethoxyisoflavanone in a 94% yield. The result is in accord with the experienced facts and the previous assumption.[10] The isoflavanone obtained above was dehydrated with acetic acid to yield 2′: 4′: 7-trimethoxyisoflavone in a 69% yield. The demethylation of 2′: 4′: 7-trimethoxyisoflavone[3,7] to 2′: 4′: 7-trihydroxyisoflavone was achieved in a 98% yield by using anhydrous aluminum chloride.[14] Since it was found that the relatively strong acidic character of the 7′-hydroxyl group prevented the use of complex metal hydride, the 7′-phenolic function of 2′: 4′: 7-trihydroxyisoflavone had to be methylated before reduction. This selective methylation of the 7′-phenolic function was accomplished in a 73% yield at 30 to 40°C using methyl iodide and potassium carbonate in acetone. The same substance was also obtained by partial methylation with diazomethane. The structure of monomethoxyisoflavone was confirmed by studying its ultraviolet spectra in neutral and alkaline solutions. Thus, as expected, the ultraviolet spectrum of 7-methoxy-2′: 4′-dihydroxyisoflavone does not reveal any appreciable bathochromic shift in an alkaline solution (Fig. 3). However, the ultraviolet spectrum of the corresponding 7-hydroxyisoflavone in an alkaline solution exhibits batho- and hypochromic shifts when compared with that in a neutral solution (Fig. 4). When the 7-methoxy-2′: 4′-dihydroxyisoflavone thus obtained was submitted to sodium borohydride reduction, it gave rise to an oily stereoisomeric mixture of 7-methoxy-2′: 4′-dihydroxyisoflavan-(4)-ols. The final step of the synthesis was accomplished as follows. The oil obtained above was refluxed with 50% acetic acid for one hour.

13) K. L. Williamson, *J. Am. Chem. Soc.*, **85**, 516 (1963).
14) W. B. Whalley, *J. Chem. Soc.*, **1953**, 3366.

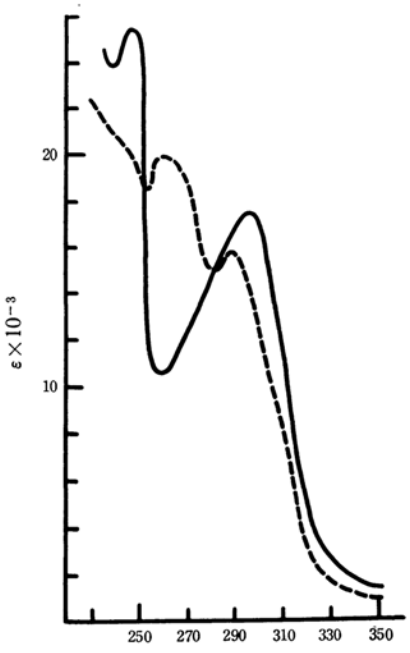


Fig. 3. Ultraviolet spectra of 7-methoxy-2′: 4′-dihydroxyisoflavone.
—— Neutral
---- In 0.1 N aq. NaOH solution

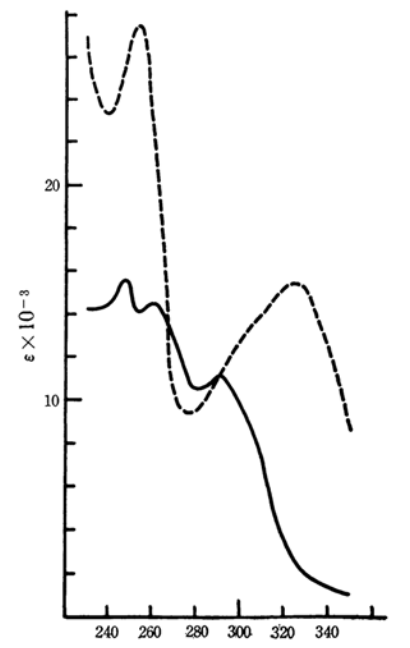
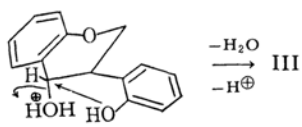


Fig. 4. Ultraviolet spectra of 7-hydroxyisoflavone.
---- 0.1 N aq. NaOH solution
—— Neutral

The product was then treated with methyl iodide and potassium carbonate in acetone for 3 hr. When the product was treated with aqueous ethanol, short needles of *d, l*-homopterocarpin, m. p. 123—125°C, was obtained in a rather poor yield. When compared with the natural specimen, m. p. 87—88°C, synthetic *d, l*-homopterocarpin showed NMR, infrared and ultraviolet spectra identical with those of natural homopterocarpin.

The aryl group in the carbon 3 of isoflavan-4-ol obtained from the reduction of the isoflavone with sodium borohydride should be almost entirely in an equatorial position. However, the hydroxyl group in the carbon 4 of diol II can be either in the quasi equatorial or quasi axial position,[15] because of the easy conformational inversion of intermediary isoflavanone during metal hydride reduction. That is, the isoflavan-4-ol obtained is a mixture of cis 3(eq.): 4(ax.) and trans 3(eq.): 4(eq.) with respect to 3 and 4-substituents. Although the SN2 mechanism of the ring formation can not be entirely excluded, the smooth formation of chromanocoumaran (III) ($R^1=R^2=R^3=H$) from isoflavan-4-ol (II) ($R^1=R^2=R^3=H$) in a high yield (70%) can perhaps be better explained by assuming the SNI character of the reaction in which the common carbonium ion is produced from the protonated form VI of cis and trans isomers, and by also assuming a simultaneous attack by the phenolic hydroxyl.



(VI)

From these considerations, it may be concluded that the reaction should produce a stable cis B/C ring junction and that, therefore, the B/C ring junction of natural homopterocarpin and the related compounds are cis.

The NMR spectrum of the synthetic *d, l*-homopterocarpin in deuteriochloroform showed a proton on position 4 as a doublet centered at $\tau=4.54$ ($J=6.0$ c. p. s.). The Karplus equation gives $\phi=55°$ for the dihedral angle HC^3–C^4H–. Assignment of other protons: $\tau=6.27$ and 6.30 (4′ and 7 methoxyls), the multiplet, $\tau=5.75$ to $\tau=6.54$ (two hydrogens on position 2 and one hydrogen on position 3), a doublet centered at $\tau=2.91$ ($J=8.6$) (a hydrogen on the position 6′) and the multiplet $\tau=3.32$—3.66 (protons on the positions 3′, 5′, 6′ and 8).

Experimental[16]

2 : 2′-Bismethoxymethoxybenzoin and 2 : 2′-Bismethoxymethoxybenzil.—Potassium cyanide (1 g.) and 2-methoxymethoxybenzaldehyde[8,17] (b. p. 112.5—115.5°C/5 mmHg, 6 g.) in 7.2 ml. of ethanol were refluxed on a water bath for 2 hr. The solvent was then removed under reduced pressure, and the oily residue was extracted with ether. The ethereal solution was washed with water and dried. After the ether had been removed, and the starting material (b. p. 103°C/3 mmHg) had been distilled, the viscous, reddish residue yielded 2 g. of a viscous, pale yellow oil boiling at 176—186°C/0.05 mmHg.[18] On standing, this oil partially crystallized. It was recrystallized from 80% ethanol, giving 2 : 2′-bismethoxybenzil; m. p. 107—107.5°C. IR: 1665 cm^{-1} and 1675 cm^{-1} (–CO-CO–).

Found: C, 64.79; H, 5.59. Calcd. for $C_{18}H_{18}O_6$: C, 65.4; H, 5.5%.

2 : 2′-Dihydroxybenzoin and 2 : 2′-Dihydroxybenzil.—The oily mixture of benzoin and benzil (1.7 g.) obtained above, in 50% acetic acid (12 ml.) containing 0.05 g. of sulfuric acid, was refluxed for 15 min. The solution was then cooled and poured into ice water containing 6 g. of sodium carbonate. The solid which separated was extracted with ether. The ethereal extract was washed with water and dried over sodium sulfate. After the solvent had been removed, the residual yellowish brown substance was recrystallized from benzene to yield 0.6 g. (m. p. 161—163°C) of benzoin.[19] IR: 1643 cm^{-1} (C=O) 3305 and 3507 cm^{-1} (OH). The filtrate from the isolation of benzoin was concentrated to yield crude benzil, which was then recrystallized from 80% ethanol. Yellow needles, m. p. 156—157°C.[20] IR: 1631 and 1614 cm^{-1} (COCO) 1635 cm^{-1} (–CO–CO–, chloroform) 3180 cm^{-1} broad, (OH). UV λ_{max} (ε_{max}): 256 (14930), 330 (6300); λ_{min} (ε_{min}): 292 (1850). This benzil (0.5 g.) in acetone (20 ml.) was refluxed with dimethylsulfate (0.5 g.) and sodium carbonate (1.5 g.) for 20 hr. After the solvent had been removed, the residue was extracted with ether, washed with water, 2 N sodium hydroxide, and water successively, and dried. The residue was then recrystallized from 80% ethanol to yield 2 : 2′-dimethoxybenzil. Colorless needles, m. p. 127—128°C.[21] IR: 1653 and 1673 cm^{-1} (–CO–CO–) 1663 cm^{-1} (–CO–CO–, chloroform). This benzil formed a quinoxaline derivative; m. p. 181.5—182.0°C.

2 : 2′-Dihydroxydesoxybenzoin and 2-(*O*-Hydroxyphenyl)-coumarone. — 2 : 2′-Dihydroxybenzoin (14 g.) in 50% ethanol (90 ml.) and 15% aqueous potassium hydroxide (150 ml.) were refluxed with powdered zinc (40 g.) for 8 hr. After the zinc had been removed and the solution had been neutralized with 2 N

15) E. M. Philbin and T. S. Wheeler, *Proc. Chem. Soc.*, **1958**, 167.

16) Melting points are uncorrected. Infrared spectra were taken in Nujol, and ultraviolet spectra were taken in ethanol unless otherwise stated. Analyses by Mr. Kusuo Narita in the Department of Pharmacy, Faculty of Medicine, Hokkaido University. NMR spectra were taken in deuteriochloroform by Japan electron optics 3H 60 high resolution NMR spectrometer. (60 Mc.) Tetramethylsilane was used as internal standard.

17) Reported b. p. 128—130°C/11 mmHg.[8]

18) Reported b. p. 200—210°C/1 mmHg.[8]

19) Reported m. p. 142—149°C.[8]

20) Reported m. p. 154—155°C. R. Kuhn, L. Birkofer and E. F. Möller, *Ber.*, **76**, 900 (1943).

21) Reported m. p. 130°C, A. Schönberg and O. Kraemer, *Ber.*, **55**, 1174 (1922).

hydrochloric acid, ethanol was evaporated under reduced pressure. The solution was extracted with ether, washed with water, and dried. The residue was then recrystallized from benzene to yield desoxybenzoin. Colorless needles; m. p. 102—103°C.[22] Yield 9.3 g. (71%). IR (KBr): 1629 cm^{-1} (–CO–CO–) 3465 cm^{-1} (OH). UV λ_{max} (ε_{max}): 327 (3060), 253 (8310); λ_{min} 293 (1360).

The filtrate was concentrated to yield crude 2-(*O*-hydroxyphenyl)-coumarone, which was then recrystallized from 80% ethanol. Feeble pink colored needles; m. p. 95—95.5°C.[23] A ferric chloride color reaction was negative. IR (KBr): 3213 cm^{-1} (broad, OH). UV λ_{max} (ε_{max}): 328 (16750), 314 (17650), 289 (12410); λ_{min} (ε_{min}): 323 (14880), 293 (10740), 249 (2320).

2′-Hydroxyisoflavone (I) ($R^1=R^2=R^3=H$).—2 : 2′-Dihydroxydesoxybenzoin (8 g.) in ethylformate (280 ml.) was added, dropwise to powdered sodium (11 g.) under ice-cooled conditions. After the solution had been set aside for three days at −5°C, the reaction mixture was slowly poured into 100 g. of ice water. The aqueous solution was neutralized with 2 N hydrochloric acid and freed from ethylformate under reduced pressure, and the solution was extracted with chloroform. The chloroform solution was washed with water and dried. After the solvent had been removed, the residue was recrystallized from methanol. Yield 6.3 g. (75.5%). Colorless plates; m. p. 153—154°C.

Found: C, 75.67; H, 4.45. Calcd. for $C_{15}H_{10}O_3$: C, 75.62; H, 4.23%. UV λ_{max} (ε_{max}): 285 (10100), 240 (24320); λ_{min} (ε_{min}): 271 (7720). IR: 1633 cm^{-1} (–CO–), 3185 cm^{-1} (OH) (broad).

2′-Hydroxyisoflavanone (IV) ($R^1=R^2=R^3=H$).—2′-Hydroxyisoflavone (2 g.) in acetic acid (110 ml.) was hydrogenated in the presence of a platinum catalyst. 220 ml. of hydrogen was thus absorbed. After the catalyst had been removed, the solvent was evaporated to dryness. The residue was thus extracted with chloroform, washed with water, and dried. After the solvent had been removed, the residue was recrystallized from 80% ethanol; m. p. 118—122°C.

Found: N, 13.27. Calcd. for $C_{21}H_{16}O_6N_4$: N, 13.33%. UV λ_{max} (ε_{max}): 318 (3400), 276 (3310), 250 (9700). IR: 1660 cm^{-1} (–CO–) 3297 cm^{-1} (broad, OH).

2, 4-Dinitrophenylhydrazone was prepared in the usual way; m. p. 223°C (decomp.); red needles.

2′-Methoxyisoflavone[24] (I) ($R^1=CH_3$, $R^2=R^3=$OMe).—2′-Hydroxyisoflavone (0.2 g.) in a mixed solvent of ether and acetone (20.3 g.) was treated with ethereal diazomethane (from nitrosomethylurea, 1.5 g.) and then set aside for 24 hr. The solution was washed with 2 N sodium hydroxide solution, and with water, and dried. After the solvent had been removed, the residue was recrystallized from methanol; m. p. 174—178°C. Yield 0.05 g. (23.6%). IR (KBr): 1642 cm^{-1} (CO). UV λ_{max} (ε_{max}): 299 (6440), 282 (6560), 240 (18850, inflection); λ_{min} (ε_{min}): 290 (5980), 270 (5280). (Found: C, 16.53; H, 5.14%.)

Chromenocoumarone (V) ($R^1=R^2=H$).—2′-Hydroxyisoflavanone (1 g.) and sulfuric acid (0.5 g.) in 50% acetic acid (100 ml.) were refluxed for 1 hr. on a heating mantle. The solvent was then removed under reduced pressure, and the residue was extracted with ether. The ethereal solution was washed with a 2 N sodium hydroxide solution, and with water, and dried over sodium sulfate. After the solvent had been removed, the residue was recrystallized from ethanol (2 ml.). Colorless needles, m. p. 87—89°C. Yield (0.55 g.) (59.4%).

Found: C, 81.21; H, 4.73. Calcd. for $C_{15}H_{10}O_2$: C, 81.06; H, 4.54%.

2′-Hydroxyisoflavan-(4)-ol (II) ($R^1=R^2=R^3=H$).—Into 2′-hydroxyisoflavone (1 g.) in dry dioxane (100 ml.), there was stirred sodium borohydride (200 mg.) in 95% ethanol (7.5 ml.) at 60 to 65°C. The solution was kept at 60 to 65°C for 1 hr. and then it was set aside overnight. After acetone (75 ml.) had been added, the solution was stirred for 15 ml. in order to destroy any excess sodium borohydride. The precipitation yielded was removed by filtration. After the solvent had been removed, the residue was extracted with chloroform, washed with water, and dried. After the chloroform had been removed, a light brown oil (0.8 g). was obtained. This oil was used for the next step without further purification.

IR (liquid film). No carbonyl absorption; a broad band around 3327 cm^{-1} (OH). UV λ_{max} (ε_{max}): 275 (3110); λ_{min} (ε_{min}) 252 (1390).

Chromanocoumaran (III) ($R^1=R^2=R^3=H$).—2′-Hydroxyisoflavan-(4)-ol (0.2 g.) in 50% acetic acid (20 ml.) was refluxed for 1 hr. After the solvent had been removed, the residue was extracted with ether (15 ml.). The ethereal solution was then washed with water (5 ml.), and dried. After the solvent had been removed, the residue was recrystallized from ethanol. Colorless needles; m. p. 126—127°C (125 mg.).

Found: C, 79.83; H, 5.49. Calcd. for $C_{15}H_{12}O_2$: C, 80.33; H, 5.39%. UV λ_{max} (ε_{max}): 278 (3260); λ_{min} (ε_{min}): 247 (590).

2 : 4-Dihydroxy-2′ : 4′-dimethoxydesoxybenzoin.[25]—This was prepared by the Hoesch reaction in the usual manner. 25 g. of 2 : 4-dimethoxyphenylacetonitrile[26] (by the procedure of Mitter and Mitra[27]) and resorcinol (35.5 g.) in the presence of zinc chloride (249 g.) in dry ether (630 ml.) yielded 25.2 g. of the desired desoxybenzoin, m. p. 152—153°C.[25]

2-Hydroxy-2′ : 4 : 4′-trimethoxydesoxybenzoin.[3]—2 : 4-Dihydroxy-2′ : 4′-dimethoxydesoxybenzoin (23.8 g.) and methyliodide (7.7 ml.) in acetone (450 ml.) were refluxed for 70 min. in the presence of potassium carbonate (30 g.) After the acetone and potassium carbonate had then been removed, the residue was recrystallized from 70% ethanol to yield 12.7 g. (51%) of the desired material, m. p. 109—113°C. The residue from the filtrates yield the corresponding tetramethoxydesoxybenzoin as colorless needles, m. p. 73.5—74.0°C (0.9 g.). A ferric chloride color reaction was negative.

2-Hydroxy-7 : 2′ : 4′-trimethoxyisoflavanone.—2-Hydroxy-7 : 2′ : 4′-trimethoxydesoxybenzoin (6.6 g.) in 178 ml. of ethylformate was added, dropwise to

22) Reported m. p. 104°C.[8]
23) Reported m. p. 95—98°C.[8]
24) W. B. Whalley and G. Lloyd, *J. Chem. Soc.*, **1956**, 3213. Reported m. p. 184°C.
25) J. M. Sehal and T. R. Seshadri, *Proc. Ind. Acad. Science*, **42A**, 36 (1955). Reported m. p. 158—159°C.
26) B. Reichert and W. Koch, *Arch. Pharm.*, **273**, 265 (1935).
27) P. C. Mitter and S. S. Mitra, *J. Ind. Chem. Soc.*, **13**, 236 (1936).

powdered sodium (6 g.), which had been cooled to −5°C, in the course of 30 min. After the reaction mixture had been set aside at 0°C for 55 hr., the deep reddish solution was poured onto ice (100 g.) and the solution was acidified with 30 ml. of 2 N hydrochloric acid. The ethyl formate layer was separated, washed with 50 ml. of water, and concentrated under reduced pressure. The crystals which separated were collected by filtration to yield 12.8 g. of nearly pure isoflavanone (m. p. 130—141°C). The concentration of the filtrate yielded a further 0.88 g. of the isoflavanone. Recrystallization from aqueous ethanol; m. p. 149—150°C.

Found: C, 65.40; H, 5.48. Calcd. for $C_{18}H_{18}O_6$: C, 65.44; H, 5.49%. IR: 1665 cm^{-1} (pyranone C=O) 3392 cm^{-1} (OH).

2′: 4′: 7-Trimethoxyisoflavone (I) (R^1=CH_3, R^2=R^3=OMe). — 2 - Hydroxy - 2′ : 4′ : 7 - trimethoxyisoflavone (11.8 g.) in acetic acid (100 ml.) was refluxed for half an hour. To the filtered solution there was then added water (170 ml.). The crystals which separated were collected by filtration; m. p. 138—142°C, 9.9 g. They were then recrystallized from 70% ethanol to yield a pure material (7.8 g.), m. p. 146—148°C.[28] IR: 1635 cm^{-1} (C=O).

2′: 4′: 7-Trihydroxyisoflavone (I) (R^1=H, R^2=R^3=OH).—2′: 4′: 7-Trimethoxyisoflavone (0.5 g.) dissolved in benzene (60 ml.) was refluxed with anhydrous aluminum chloride (5.5 g.) for two hours on a water bath. The supernatant benzene was removed by decantation and then under reduced pressure. The residual benzene-free complex was decomposed with ice-cooled water. The precipitation was collected by filtration and dissolved in methanol (40 ml.). Upon the concentration of the above solution to approximately 5 ml., 2′: 4′: 7-trihydroxyisoflavone (0.42 g.) was separated; m. p. 272°C (decomp.). IR: 1617 cm^{-1} (C=O), associated OH 3400 cm^{-1}. UV λ_{max} (ε_{max}): 248 (15600), 262 (14500), 292 (11110). UV 0.1 N sodium hydroxide solution λ_{max} (ε_{max}): 254 (27400), 325 (15390).

Found: C, 63.64; H, 4.01. Calcd. for $C_{15}H_{10}O_5$: C, 66.67; H, 3.73%.

2′: 4′: 7-Triacetoxyisoflavone (I) (R^1=$COCH_3$, R^2=R^3=$OCOCH_3$).—This was prepared in the usual way; m. p. 148—150°C. (from 80% ethanol). Yield 70%.

Found: C, 63.50; H, 4.30. Calcd. for $C_{21}H_{16}O_8$: C, 63.63; H, 4.07%.

7-Methoxy-2′: 4′-dihydroxyisoflavone (I) (R^1=H, R^2=OH, R^3=OCH_3).—a) 2′ : 4′ : 7-Trihydroxyisoflavone (1 g.) and methyl iodide (1 g.) in acetone (100 ml.) were treated with potassium carbonate (2 g.) at 30—40°C for 10 hr. while being stirred. After the potassium carbonate and acetone had been removed, the residue was recrystallized from 80% alcohol (25 ml.), thus yielding 7-methoxy-2′: 4′-dihydroxyisoflavone (767 mg.) m. p. 207—208°C.

Found: 63.92; H, 4.83. Calcd. for $C_{16}H_{12}O_5 \cdot H_2O$: C, 63.57; H, 4.67%. Water of crystallization. Found: 5.93. Calcd.: 5.96%.

IR: 1625 cm^{-1} (C=O), 3490, 3420 and 3135 cm^{-1} (associated OH).

UV λ_{max} (ε_{max}): 260 (19800), 290 (15650).

UV 0.1 N sodium hydroxide λ_{max} (ε_{max}) solution: 250 (25400), 297 (17400).

28) Reported m. p. 148—149°C.[8]

b) To 2′ : 4′ : 7-Trihydroxyisoflavone (49 mg.) in acetone (10 ml.) there was added ethereal diazomethane (from 80 mg. of nitrosomethylurea) (15 ml.). The solution was then set aside for 24 hr. and 40 min. After the solvent and diazomethane, had been removed, the residue (46 mg.) was recrystallized from 80% ethanol (1 ml.), thus yielding 27 mg. of yellow needles, m. p. 206—207°C. This material was identical with the 7-methoxy-2′: 4′-dihydroxyisoflavone obtained by procedure a).

7-Methoxy-2′: 4′-dihydroxyisoflavan-(4)-ol, (II) (R^1=H, R^2=OH, R^3=OCH_3).—Sodium borohydride (200 mg.) in 95% alcohol (25 ml.) was added, dropwise to a solution of 7-methoxy-2′: 4′-dihydroxyisoflavone (680 mg.) in dioxane (45 ml.) at 60—65°C. The reaction mixture was kept for 1 hr. at 60—65°C and then set aside overnight at room temperature. After acetone (5 ml.) had been added to decompose the excess reducing reagent, the solvents were removed under reduced pressure, and the residue was extracted with ether (25 ml.) and water (20 ml.). The ethereal layer was washed with water and dried. After the solvent had been removed, the light-brown, oily isoflavan-4-ol (457 mg., 67%) was obtained.

UV λ_{max} (ε_{max}): 280 (5500); λ_{min} (ε_{min}): 248 (248).

IR (liquid film), no carbonyl absorption. Broad band around 3300 cm^{-1} (OH).

***d, l*-Homopterocarpin (III) (R^1=R^3=OCH_3, R^2=H).**—The oil obtained above was refluxed with 50% acetic acid (11 ml.) for one hour, and then the solvents were removed under reduced pressure. The ultraviolet spectrum (Fig. 5) of the residue (438 mg.) exhibited two maxima, at 286 mμ (ε, 6900) and at 325 mμ (ε, 3130). The latter is due to the presence of isoflav-3-ene in the product. The residue was refluxed with

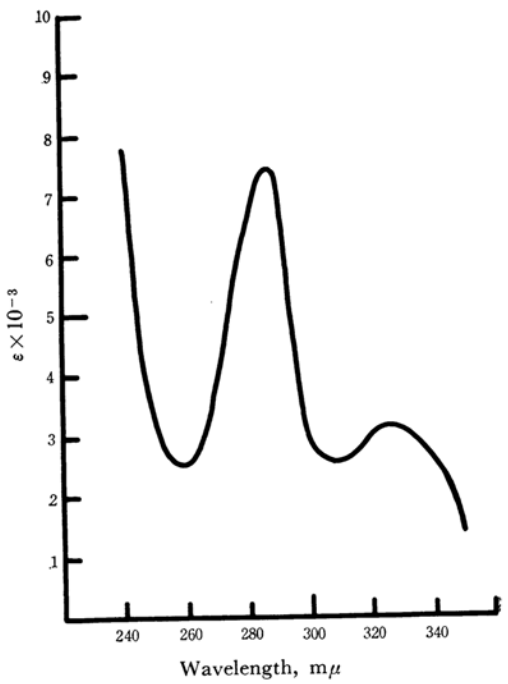


Fig. 5.

methyl iodide (4 g.) and potassium carbonate (2 g.) in acetone (20 ml.) for three hours. After the potassium carbonate and acetone had been removed, the residue was extracted with ether (25 ml.) and with water (20 ml.); after extraction with a 2 N aqueous sodium hydroxide solution (10 ml.), the dried ethereal solution yielded a light yellow oil (219 mg.). This oil in acetone (50 ml.) was refluxed with Norit (100 mg.) for 1 hr. The removal of Norit and acetone left the residue (84 mg.). This was chromatographed on Merck acid-washed alumina (5 g.). The first elution (27 mg.), with benzene (20 ml.), yielded 27 mg. of *d, l*-homopterocarpin (121—124.5°C). A further 9 mg. of the substance was obtained by the elution of Norit with acetone (30 ml.). On recrystallization from ethanol, colorless short needles of *d, l*-homopterocarpin (m. p. 123—125°C) were obtained. Its infrared spectrum in chloroform and its ultraviolet spectrum were superimposable upon those of a natural specimen. UV λ_{max} (ε_{max}): 286 (9200).

Found: C, 71.72; H, 5.59. Calcd. for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67%.

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