Isoflavonoids of the Bark of *Dipteryx odorata* Willd. (Aubl.)

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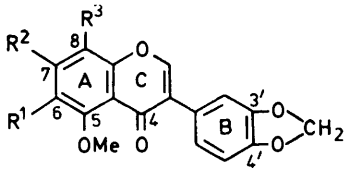
The two new isoflavones, dipteryxine and odoratine, isolated from the bark of *Dipteryx odorata* Willd. (Aubl.), have been established as 5,6-dimethoxy-7-hydroxy-3',4'-methylenedioxyisoflavone (1a) and 3',4'-methylenedioxy-5,6,7-trimethoxyisoflavone (1b), respectively, by means of spectroscopic as well as chemical evidence, and by synthesis.

THE black, fragrant seeds, known as Tonka beans, of *Dipteryx odorata* Willd. (Aubl.) (common name, Sarrapia in Venezuela or Cumaru in Brazil) have been investigated from a chemical point of view by earlier workers,[1] and they have been recognised for a long time as a rich source of coumarin, which is important in perfumery industries. However, so far practically no chemical work has been done on the constituents of the bark of this plant.†

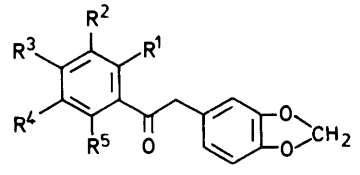
RESULTS AND DISCUSSION

We have isolated from this bark two new isoflavones, dipteryxine and odoratine,‡ besides lupeol, betulin, and a mixture of methyl esters of fatty acids.[3] Dipteryxine has a molecular formula, $C_{18}H_{14}O_7$, and odoratine,

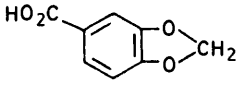


(1)

a ; R^1 = OMe , R^2 = OH , R^3 = H
b ; R^1 = R^2 = OMe , R^3 = H
c ; R^1 = H , R^2 = R^3 = OMe
d ; R^1 = R^3 = OMe , R^2 = H
e ; R^1 = OH , R^2 = OMe , R^3 = H
f ; R^1 = OEt , R^2 = OMe , R^3 = H



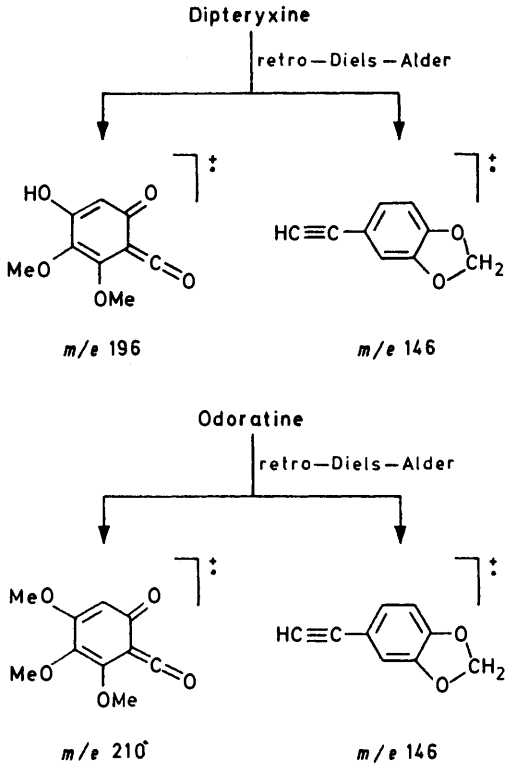
(2)



(3)

a ; R^1 = R^3 = OH , R^2 = H , R^4 = R^5 = OMe
b ; R^1 = OH , R^2 = R^3 = R^5 = OMe , R^4 = H
c ; R^1 = R^2 = R^3 = OMe , R^4 = H , R^5 = OH
d ; R^1 = R^3 = OMe , R^2 = OEt , R^4 = H , R^5 = OH

$C_{19}H_{16}O_7$, and the i.r. and u.v. spectra indicated that they are either isoflavonoid or flavonoid derivatives (see Experimental section). The ^{1}H n.m.r. spectra revealed the presence of one phenolic hydroxyl, one methylenedioxy, and two methoxyl groups in dipteryxine, and one methylenedioxy and three methoxyl groups in odoratine (see Experimental section). Since methylation of the phenolic hydroxyl group of dipteryxine yields odoratine, the latter is the *O*-methyl ether of



the former. Dipteryxine is hydrolysed to the deoxybenzoin derivative (2a) under mild alkaline conditions, thereby clarifying it to be an isoflavonoid instead of a flavonoid derivative. Examination of the mass spectrometric fragmentation patterns[4] disclosed that in dipteryxine, the methylenedioxy-group is located on ring B, and the two methoxyl groups and the phenolic hydroxyl group are on ring A, whereas in odoratine, the three methoxyl groups are on ring A. The position of the methylenedioxy-group on ring B was further determined to be between C-3' and C-4' by the alkaline hydrogen peroxide oxidation of dipteryxine to piperonylic acid (**3**).

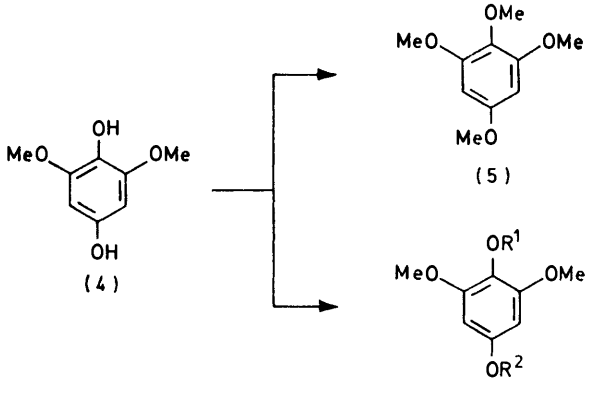
In the ^{1}H n.m.r. spectra of dipteryxine and odoratine,

† Recently, a report on the constituents of the heartwood of this plant has appeared (T. Hayashi and R. H. Thomson, *Phytochemistry*, 1974, **13**, 1943).

‡ The names dipteryxine and odoratine, have been assigned to isoflavone A, $C_{18}H_{14}O_7$, and isoflavone B, $C_{19}H_{16}O_7$, respectively (see ref. 2).

one of the two methoxyl groups resonates at somewhat low field, δ 4.01 and 3.95, respectively, indicating that it may be located at C-5, which is *peri* to the carbonyl group at C-4. In the ^{1}H n.m.r. spectrum of dipteryxine, no hydroxyl proton, which is hydrogen-bonded (δ >10) to the carbonyl group at C-4, could be detected, and so its phenolic hydroxyl group should not be located at C-5. In the ^{13}C n.m.r. spectra of dipteryxine, its *O*-acetyl derivative, and odoratine, the signals for the two methoxyl carbons appear at low field (δ >60) relative to the ordinary methoxyl carbons. According to the rule for the methoxyl-carbon shift, as established for *ortho*-disubstituted anisole derivatives in a preliminary communication,[2] each of these two methoxyl groups in their molecules should bear two *ortho*-substituents, thereby excluding structure (1e) for dipteryxine and structure (1c) for odoratine. Therefore, only structures (1a) and (1b) are conceivable for dipteryxine and odoratine, respectively.*

At an early date, Campbell and Tannock [5] isolated a new isoflavone from *Cordyla africana* and assigned to it structure (1b) solely on the basis of ^{1}H n.m.r. and mass-spectroscopic evidence. Professor Tannock kindly compared a sample of odoratine with that of his compound (i.r.) and informed us that they are not identical. Therefore, in order to clarify this discrepancy, we attempted to synthesise compound (1b) and its related compound (1c).



a ; R^1 = Me , R^2 = H
b ; R^1 = Me , R^2 = CH_2Ph
c ; R^1 = Et , R^2 = H
d ; R^1 = Et , R^2 = CH_2Ph

For this purpose, 1,2,3-trimethoxybenzene [6] was employed as a starting material. This trimethoxybenzene was oxidised with nitric acid to 2,6-dimethoxy-*p*-benzoquinone,[7] which was then reduced with sodium hydrosulphite [8] to 1,3-dimethoxy-2,5-dihydroxybenzene (4). As is apparent in the sequel, compound (4) served as a common intermediate for the syntheses of both compounds (1b) and (1c). Methylation of compound (4) with dimethyl sulphate and alkali under the condition of Chapman *et al.*[6] furnished 1,2,3,5-tetramethoxybenzene (5) and a trimethoxyphenol † in a ratio of *ca.* 2 : 1. That the above trimethoxyphenol was not 2-hydroxy-1,3,5-trimethoxybenzene but was in fact (6a), was supported by the subsequent sequence of reactions,‡ and also by the ^{13}C n.m.r. spectrum.

As shown in the Table, all the δ values of the aromatic carbons observed for this trimethoxyphenol are compatible with those calculated for structure (6a). Furthermore, the δ value of the methoxyl carbon at C-2 appears at a low field of δ 61.1 [2] This is in keeping with the downfield shift rule of the δ values of the methoxyl carbons which has been established for *ortho*-disubstituted anisole derivatives.

^{13}C N.m.r. spectra of substituted benzenes [a]
[δ_C values in p.p.m. from internal $SiMe_4$ in $CDCl_3$]

		Calculated [b]	Observed
1,2,3,5-Tetramethoxybenzene	C-1 (3)	147.4	153.8
	C-2	123.3	132.5
	C-4 (6)	92.9	91.9
	C-5	154.1	156.4
	1-MeO (3)		56.1
	2-MeO		61.0
	5-MeO		55.5
5-Hydroxy-1,2,3-trimethoxybenzene	C-1 (3)	147.8	153.8
	C-2	123.7	131.7
	C-4 (6)	107.3	93.2
	C-5	149.6	152.8
	1-MeO (3)		56.1
	2-MeO		61.1
2-Hydroxy-1,3,5-trimethoxybenzene	C-1 (3)	149.1	
	C-2	118.8	
	C-4 (6)	93.3	
	C-5	155.0	
1,3-Dimethoxy-2-ethoxy-5-hydroxybenzene	C-1 (3)		154.0
	C-2		130.1
	C-4 (6)		93.2
	C-5		152.9
	1-MeO (3)		55.9
	CH_3CH_2O		15.3
	CH_3CH_2O		69.3
1,3-Dimethoxy-5-ethoxy-2-hydroxybenzene	C-1 (3)		147.5
	C-2		129.3
	C-4 (6)		92.8
	C-5		152.5
	1-MeO (3)		56.3
	CH_3CH_2O		14.9
	CH_3CH_2O		64.1

[a] Natural-abundance ^{13}C Fourier-transform n.m.r. spectra were recorded on a Varian NV–14 FT n.m.r. spectrometer at 15.087 MHz using about 1 mmol cm^{-3} solutions in $CDCl_3$ and 8-mm spinning tubes at room temperature; errors of δ (from internal $SiMe_4$) are *ca.* ±0.1. We thank Dr. Tori, Shionogi Research Laboratory, Shionogi and Co., Ltd., Osaka, Japan, for these determinations. [b] See G. C. Levy and G. L. Nelson, 'Carbon-13 Nuclear Magnetic Resonance for Organic Chemists,' Wiley–Interscience, New York, 1972, p. 81.

Condensation of 1,2,3,5-tetramethoxybenzene (5) with 3,4-methylenedioxyphenylacetyl chloride by the

* Benzene-induced shift (ASIS) studies of the ^{1}H n.m.r. spectra of odoratine, and the *O*-acetyl and the *O*-ethyl derivatives of dipteryxine, showed that one of the methoxyl signals was shifted slight downfield while the other methoxyl signals underwent an upfield shift. These observations indicated that one of the methoxyl groups in odoratine and dipteryxine should be situated at C-5, having a substituent at C-6 (see R. G. Wilson, J. H. Bowie, and D. H. Williams, *Tetrahedron*, 1968, **24**, 1407). This ASIS behaviour of the methoxyl signals is also compatible with the structures proposed.

† Under these methylation conditions, another trimethoxyphenol, 2-hydroxy-1,3,5-trimethoxybenzene, was not isolated.

‡ Note that if this trimethoxyphenol were 2-hydroxy-1,3,5-trimethoxybenzene, then the product obtained after its Friedel–Crafts reaction could not be cyclised to an isoflavone derivative,

Friedel–Crafts method yielded a phenylbenzyl ketone in 54% yield. In its ^{1}H n.m.r. spectrum, three instead of four methoxyl groups [δ 3.78 (3 H, s), 3.85 (3 H, s) and 3.98 (3 H, s)] were observed. Furthermore, a hydroxyl proton hydrogen-bonded to the carbonyl group was also detected at δ 13.22. It appears, therefore, that the hydrolysis of one of the methoxyl groups *ortho* to the carbonyl group occurred when the reaction was treated with hydrochloric acid. That this phenylbenzyl ketone was (2b) rather than (2c) was evident, since if the latter were the case, then the isoflavone obtained after its subsequent ring-closure would be identical with 3′,4′-methylenedioxy-5,6,7-trimethoxyisoflavone (1b) which was to be synthesised later (see below).*

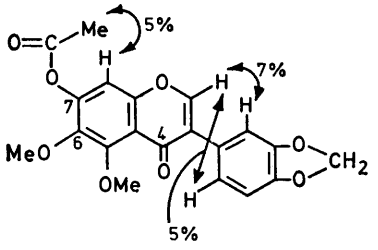
Cyclisation of compound (2b) was effected by sodium and ethyl formate, followed by acetic anhydride, to give 3′,4′-methylenedioxy-5,7,8-trimethoxyisoflavone (1c) in 63% yield. Direct comparison showed that this compound was not identical with odoratine.

For the synthesis of compound (1b), compound (6a) was converted into the benzyl ether (6b) and the latter was allowed to react with 3,4-methylenedioxyphenylacetyl chloride by the Friedel–Crafts procedure. In this case, in order to avoid the hydrolysis of a methoxyl group, the reaction complex was treated with 1% aqueous hydrochloric acid at 0 °C. Under these conditions, only the benzyl group was hydrolysed and the methoxyl group in question remained intact, and the desired compound (2c) was obtained in 45% yield. Ring-closure of compound (2c) using the same ethyl formate–sodium method as before afforded in 61% yield 3′4′-methylenedioxy-5,6,7-trimethoxyisoflavone (1b). Direct comparison with odoratine established its identity.

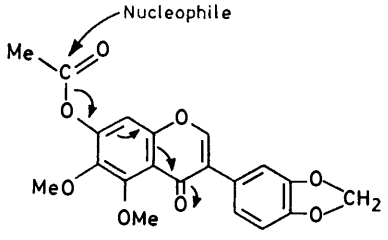
Since the structure of odoratine has been unequivocally established as (1b) † by synthesis, dipteryxine must be formulated as (1a).

Further spectroscopic evidence favouring structure (1a) over (1e) for dipteryxine was provided by the nuclear Overhauser effect (NOE) measurements on the *O*-acetyl derivative of dipteryxine. As indicated below, an enhancement in the proton signal at C-8 of 5% was observed when the acetyl methyl protons were irradiated under NOE conditions.‡

Since if the acetyl group were located at C-6 instead of C-7 [see structure (1e)], no NOE would be observed between the acetyl methyl protons and the proton at C-8, structure (1a) may be more appropriate for dipteryxine. Other evidence supporting this is the great susceptibility of this acetyl group to hydrolysis. Even on refluxing with methanol in the absence of added alkali for 1 d, it hydrolyses in 60% yield to the original dipteryxine. When set aside in benzene solution over Merck standard-ised alumina, activity II—III, for 1—2 d, it also hydrolyses completely. This unusual susceptibility to hydrolysis may be rationalised if it is assumed that the acetoxy group is located *para* to the isoflavone carbonyl group.



To provide additional complementary evidence, we decided to synthesise the *O*-ethyl derivative of either (1a) or (1e) and compare it with the corresponding derivative of dipteryxine. Since the synthesis of the *O*-ethyl derivative (1f) is much easier than that of the *O*-ethyl derivative of compound (1a), we attempted to synthesise



the former *via* the same sequence of reactions as before. Ethylation of compound (4) with diethyl sulphate and alkali under the same conditions as employed for the methylation yielded the desired 1,3-dimethoxy-2-ethoxy-5-hydroxybenzene (6c) in 52% yield.§ The structure of this compound was also apparent,¶ but was further confirmed by the ^{13}C n.m.r. spectrum. As shown in the Table, all the δ values of the aromatic ring carbons are compatible with those observed for the corresponding trimethoxyphenols. After conversion of compound (6c) to compound (6d) by benzylation, compound (2d) was prepared in 56% yield by condensation with 3,4-methylenedioxyphenylacetyl chloride. Ring-closure of compound (2d) then furnished in 68% yield 5,7-dimethoxy-6-ethoxy-3′,4′-methylenedioxyisoflavone (1f). As expected, this compound proved to be non-identical with the *O*-ethyl derivative of dipteryxine.

EXPERIMENTAL

M.p.s were taken on a Kofler hot-stage apparatus. Unless otherwise specified, i.r. spectra were recorded for

* For similar cases in which the demethylation of methoxy groups situated *ortho* to the entering carbonyl group in a Friedel–Crafts reaction has been observed, see M. L. Dhar and T. R. Seshadri, *Tetrahedron*, 1959, **7**, 77; and A. J. Quillinan and F. Scheinmann, *J.C.S. Perkin I*, 1973, 1329.

† Therefore, the isoflavone isolated by Tannock *et al.* has been proven not to have structure (1b).

‡ The NOE experiments were performed with a Varian HA–100 spectrometer on a degassed solution of the sample in deuteriated chloroform, as previously described (K. Takeda, K. Tori, I. Horibe, M. Ohtsuru, and H. Minato, *J. Chem. Soc.* (*C*), 1970, 2697). Estimated errors for NOE values are ±2% or less. We thank Dr. Tori for these determinations.

§ In this case, a small amount of 1,3-dimethoxy-5-ethoxy-2-hydroxybenzene was also isolated. For its ^{13}C n.m.r. spectrum, see the Table.

¶ Note that if this compound were 1,3-dimethoxy-5-ethoxy-2-hydroxybenzene, then the product obtained after its Friedel–Crafts reaction could not be cyclised to an isoflavone derivative.

potassium bromide discs with a Perkin-Elmer 337 spectrometer, and ^{1}H n.m.r. spectra with a Varian A-60 or a Bruker WP-60 (60 MHz) spectrometer for solutions in $CDCl_3$. Some ^{1}H n.m.r. spectra were determined with a Varian HA-100 (100 MHz) spectrometer. Chemical shifts are reported as δ/p.p.m. using tetramethylsilane as internal standard. Abbreviations s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. U.v. spectra were measured on a Pye–Unicam SP 1800 instrument for ethanol solutions. Mass spectra were taken with a Hitachi–Perkin-Elmer RMU 6E or a DuPont 21-492B mass spectrometer at 70 eV using a direct inlet system. Only relevant ions in the mass spectra are listed and their relative intensities are indicated in parentheses as a percentage of the base peak (DuPont 21-492B instrument). Unless otherwise specified, Merck standardised alumina, activity II—III or silica gel 60 was used for column chromatography. Thin layer chromatograms were prepared on silica gel G (Merck) and the spots were observed by exposure to iodine vapour. All organic extracts were dried over anhydrous sodium sulphate and evaporated under reduced pressure below 60 °C. Microanalyses were carried out by A. Bernhardt microanalytical laboratory, 5251 Elbach über Engelskirchen, West Germany.

Isolation of Dipteryxine and Odoratine.—The combined phenolic and neutral fractions [3] of the bark of *Dipteryx odorata* Willd. (Aubl.) (32 g) were chromatographed over silica gel (640 g). Elution with benzene and benzene–chloroform yielded the fractions of odoratine and dipteryxine respectively. Repeated chromatography of each fraction over silica gel furnished pure *odoratine* (0.1 g) and *dipteryxine* (1 g). Dipteryxine had m.p. 235—237 °C (from chloroform–ether); $\lambda_{max.}$ 208 (log ε 4.59), 220sh (4.50), 262 (4.30), and 292sh nm (4.28); $\nu_{max.}$ 3180 (OH), 1 635 (γ-pyrone CO), 1 625, 1 585, and 1 500 cm^{-1} (aromatic C=C); δ 3.93 (3 H, s, OMe), 4.01 (3 H, s, 5-OMe), 5.95 (2 H, s, OCH_2O), 6.43 (1 H, s, OH), 6.80—7.11 (3 H, m, H-2′,5′, and 6′), 6.75 (1 H, s, H-8), and 7.76 (1 H, s, H-2); *m/e* 342 (M^+), 313, 299, 269, 241, 196, 181, 163, 156, 146, and 145 (Found: C, 63.35; H, 4.25; O, 32.55. $C_{18}H_{14}O_7$ requires C, 63.16; H, 4.12; O, 32.72%). Odoratine had m.p. 172—174 °C (from chloroform–ether); $\lambda_{max.}$ 207 (log ε 4.73), 264 (4.65), and 292sh nm (4.44); $\nu_{max.}$ 1 645 (γ-pyrone CO), 1 620, 1 600, and 1 503 cm^{-1} (aromatic C=C); δ 3.89 (3 H, s, OMe), 3.93 (3 H, s, OMe), 3.95 (3 H, s, 5-OMe), 5.95 (2 H, s, OCH_2O), 6.66 (1 H, s, H-8), 6.83—7.11 (3 H, m, H-2′,5′, and 6′), and 7.77 (1 H, s, H-2); *m/e* 356 (74) (M^+), 341 (100), 327 (5), 313 (6), 298 (7), 283 (6), 211 (6), 210 (2), 195 (8), 163 (58), 146 (25), and 145 (15) (Found: C, 64.25; H, 4.70; O, 31.35. $C_{19}H_{16}O_7$ requires C, 64.04; H, 4.53; O, 31.43%).

Methylation of Dipteryxine.—Dipteryxine (500 mg), dimethyl sulphate (3 ml), anhydrous potassium carbonate (5 g), and dry acetone (70 ml) were refluxed for 24 h. Water was then added, and the product was extracted with chloroform. The O-*methyl derivative* (0.41 g) was obtained pure after recrystallisation from chloroform–ether to show m.p. 173—174 °C, identical with odoratine (i.r., u.v., ^{1}H n.m.r., and mass spectra, and mixed m.p.).

Ethylation of Dipteryxine.—To a solution of dipteryxine (500 mg) in dry acetone (70 ml) were added diethyl sulphate (3 ml) and anhydrous potassium carbonate (5 g). The mixture was refluxed for 24 h, then water was added and the product was extracted with chloroform. Removal of the chloroform yielded the O-*ethyl derivative* (0.36 g), m.p. 155—157 °C (from ether), δ(100 MHz) 1.52 (3 H, t, *J* 7 Hz, OCH_2CH_3), 3.89 (3 H, s, 6-OMe at C-6), 3.95 (3 H, s, 5-OMe at C-5), 4.15 (2 H, q, *J* 7 Hz, OCH_2CH_3), 5.95 (2 H, s, OCH_2O), 6.64 (1 H, s, H-8), 6.81 (1 H, d, $J_{5',6'}$ 8 Hz, H-5′), 6.93 (1 H, dd, $J_{6',5'}$ 8, $J_{6',2'}$ 1.5 Hz, H-6′), 7.07 (1 H, d, $J_{2',6'}$ 1.5 Hz, H-2′), and 7.76 (1 H, s, H-2); $\nu_{max.}$ 1 632 (γ-pyrone CO) and 1 598 cm^{-1} (aromatic C=C); *m/e* 370 (M^+) (Found: C, 64.75; H, 4.65; O, 30.05. $C_{20}H_{18}O_7$ requires C, 64.86; H, 4.90; O, 30.24%).

Acetylation of Dipteryxine.—Dipteryxine (0.52 g) in anhydrous pyridine (15 ml) was heated under reflux with acetic anhydride (15 ml) for 3 h. After addition of water, the product was extracted with chloroform. Crystallisation from chloroform–ether yielded the O-*acetyl derivative* (0.33 g), m.p. 165—168 °C; $\nu_{max.}$ 1 765 (acetate CO), 1 627 (γ-pyrone CO), and 1 601 cm^{-1} (aromatic C=C); δ(100 MHz) 2.36 (3 H, s, COMe), 3.91 (3 H, s, 6-OMe), 3.96 (3 H, s, 5-OMe), 5.96 (2 H, s, OCH_2O), 6.83 (1 H, d, $J_{5',6'}$ 8 Hz, H-5′), 6.93 (1 H, dd, $J_{6',5'}$ 8 ,$J_{6',2'}$ 1.5 Hz, H-6′), 6.99 (1 H, s, H-8), 7.06 (1 H, d, $J_{2',6'}$ 1.5 Hz, H-2′), and 7.82 (1 H, s, H-2); *m/e* 384 (M^+) (Found: C, 62.45; H, 4.0; O, 33.25. $C_{20}H_{16}O_8$ requires C, 62.50; H, 4.20; O, 33.30%).

Hydrolysis of Dipteryxine with Barium Hydroxide.—Dipteryxine (400 mg), barium hydroxide (2 g), and water (30 ml) were refluxed for 2 h under nitrogen. The mixture was then acidified and extracted with chloroform. The chloroform extract was washed with water and evaporated to yield the *deoxybenzoin derivative* (2a) (200 mg), m.p. 149—151 °C (from chloroform–methanol); $\lambda_{max.}$ 205 (log ε 4.47), 220sh (4.26), 240sh (4.11), 286 (4.18), and 340 nm (3.74); $\nu_{max.}$ 3 575 (OH), 1 620 (CO conjugated with the benzene ring), 1 580, 1 480, 1 455, 1 440, and 1 420 cm^{-1} (aromatic C=C), δ 3.85 (3 H, s, 3-OMe), 3.96 (3 H, s, 2-OMe), 4.28 (2 H, s, $COCH_2Ph$), 5.96 (2 H, s, OCH_2O), 6.33 (1 H, s, H-5), 6.60 (1 H, br s, OH), 6.78 (3 H, br s, H-2′,5′, and 6′), and 13.16 (1 H, s, CO • • • HO); *m/e* 332 (M^+), 197, 182, 167, and 135 (Found: C, 61.2; H, 4.65; O, 33.55. $C_{17}H_{16}O_7$ requires C, 61.44; H, 4.85; O, 33.70%).

Hydrolysis of the O-Acetyl Derivative of Dipteryxine.—(*a*) *With methanol.* The *O*-acetyl derivative (50 mg) was heated under reflux with methanol (3 ml). The reaction was monitored by t.l.c. (silica gel G). After 24 h, about 60% of the *O*-acetyl derivative had been hydrolysed to dipteryxine.

(*b*) *With alumina.* The *O*-acetyl derivative (67 mg) in benzene was set aside in contact in a column with Merck standardised alumina, activity II—III. After 1—2 d, the column was eluted with chloroform and then chloroform–methanol, which gave dipteryxine in 100% yield.

Oxidation of Dipteryxine with alkaline Hydrogen Peroxide.—To a solution of dipteryxine (200 mg) in methanol (20 ml) under reflux, a solution of potassium hydroxide (0.25 g) in water (5 ml) was added in small portions (1 ml every 30 min), followed by the addition of small quantities of hydrogen peroxide (30%, 1 ml at a time, total 5 ml) in the course of 4 h. The solution was tested occasionally to ensure that it remained alkaline. After being set aside for 12 h at room temperature, the mixture was freed from methanol under reduced pressure, and the alkaline solution was extracted with ether, acidified, and extracted with ethyl acetate. The ethyl acetate solution was passed through a silica gel column. Evaporation of the ethyl acetate and subsequent sublimation of the residue at *ca.* 210 °C yielded an acid (40 mg), m.p. 227 °C, identical with an authentic sample of 3,4-methylenedioxybenzoic acid (3) (i.r. and mixed m.p.).

Methylation of 2,5-*Dihydroxy*-1,3-*dimethoxybenzene* (4) *with Dimethyl Sulphate and Alkali*.—Compound (4) (20 g) was dissolved in a solution of sodium hydroxide (20 g) in water (140 ml) under an atmosphere of nitrogen. To this solution was added in one portion dimethyl sulphate (15 g with vigorous stirring, and after the addition the mixture was refluxed for 1 h. Water (200 ml) was then added and the solution was cooled to 0 °C whereupon 1,2,3,5-tetramethoxybenzene (5) precipitated out as a solid (6.1 g). Upon recrystallisation from hexane–benzene (7 : 3) it had m.p. 41 °C (lit.,[6] m.p. 47 °C). The alkaline filtrate from the initial precipitate of tetramethoxybenzene was neutralised with sulphuric acid, whereby 5-hydroxy-1,2,3-trimethoxybenzene (6a) (13.5 g) crystallised out. It was recrystallised from benzene, m.p. 144 °C (lit.,[6] m.p. 146 °C).

Friedel–Crafts Reaction of Compound (5) *with* 3,4-*Methylenedioxyphenylacetyl Chloride*.—Under an atmosphere of dry nitrogen 3,4-methylenedioxyphenylacetic acid (1.0 g) in anhydrous benzene (10 ml) was stirred with thionyl chloride (1 ml) at room temperature for 30 min, and the mixture was then refluxed for 1.5 h. After removal of the excess of reagent and benzene under reduced pressure, 3,4-methylenedioxyphenylacetyl chloride was distilled at the bath temperature of 118—120 °C (8 mmHg) as a viscous oil (1.0 g).

Under an atmosphere of dry nitrogen compound (5) (1 g) in anhydrous ether (20 ml) was added to a solution of anhydrous aluminium chloride (2 g) in anhydrous ether (20 ml), followed by the above phenylacetyl chloride (1 g) in anhydrous ether (10 ml). The mixture was cooled to 0 °C in ice and stirred for 3 h. Stirring was then discontinued and the mixture was set aside for an additional 12 h. Ether was then removed from the precipitated oily product by decantation, and the oil was washed with anhydrous ether (3 ×) and then treated with 15% aqueous hydrochloric acid (20 ml) at 0 °C. The product was extracted with ether and the ether extract was washed with aqueous sodium bicarbonate and then with water. After removal of the ether the residue was chromatographed over silica gel and elution with hexane–benzene (1 : 1) yielded the *phenylbenzyl ketone* (2b) (0.95 g). After crystallisation from ethanol it had m.p. 103 °C (yield, 54%), δ 3.78 (3 H, s, OMe), 3.85 (3 H, s, OMe), 3.98 (3 H, s, 6-OMe), 4.26 (2 H, s, $COCH_2Ph$), 5.90 (2 H, s, OCH_2O), 6.22 (1 H, s, H-5), 6.72 (3 H, br s, H-2′,5′, and 6′), and 13.22 (1 H, s, CO • • • HO); *m/e* 346 (10) (M^+), 211 (88), 183 (100), and 135 (46) (Found: C, 62.15; H, 5.35. $C_{18}H_{18}O_7$ requires C, 62.42; H, 5.24%).

Synthesis of 3′,4′-*Methylenedioxy*-5,7,8-*trimethoxyisoflavone* (1c).—A suspension of powdered sodium (200 mg) in dry ethyl formate (40 ml) was added under an atmosphere of dry nitrogen to a solution of compound (2b) (200 mg) in dry ethyl formate (40 ml). The mixture was stirred at 0 °C for 12 h, and then water (10 ml) was added gradually at 0 °C and the product was extracted with ether. The ether extract was evaporated under reduced pressure and the residue was refluxed with acetic anhydride (5 ml) for 1 h. After removal of the acetic anhydride under reduced pressure, the crude product was purified by chromatography over silica gel. Elution with benzene yielded the *isoflavone* (1c) (130 mg, yield, 63%), which upon recrystallisation from acetone had m.p. 181 °C; $\lambda_{max.}$ 207 (log ε 4.52), 226sh (4.37), 262 (4.53), and 294sh nm (4.10); $\nu_{max.}$ 1 670 (γ-pyrone CO), 1 630, 1 601, and 1 575 cm^{-1} (aromatic C=C), δ 3.89 (3 H, s, OMe), 3.94 (3 H, s, OMe), 3.98 (3 H, s, 5-OMe), 5.94 (2 H, s, OCH_2O), 6.43 (1 H, s, H-6), 6.81—7.13 (3 H, m, H-2′,5′, and 6′), and 7.80 (1 H, s, H-2); *m/e* 356 (100) (M^+), 341 (65), 327 (13), 313 (17), 298 (20), 283 (9), 211 (2), 210 (2), 195 (6), 163 (45), 146 (20), and 145 (13) (Found: C, 63.85: H, 4.35; O, 31.10. $C_{19}H_{16}O_7$ requires C, 64.04; H, 4.53; O, 31.43%). The i.r. spectrum of this compound was different from that of odoratine. A mixed m.p. determination also showed a depression.

5-*Benzyloxy*-1,2,3-*trimethoxybenzene* (6b).—To a solution of compound (6a) (15 g) in dry acetone (150 ml) were added anhydrous potassium carbonate (15 g), benzyl chloride (10 g), and sodium iodide (2 g). The mixture was heated under reflux for 6 h under an atmosphere of dry nitrogen. After filtration from inorganic materials, the solution was evaporated at 90 °C under reduced pressure to remove the excess of reagent, and the residue was chromatographed over Woelm basic alumina, activity I. Elution with hexane–benzene (1 : 1) afforded the *benzyl ether* (6b) (17.1 g, 74%), which after recrystallisation from hexane–benzene (7 : 3) had m.p. 53 °C, δ 3.83 (9 H, s, OMe), 5.02 (2 H, s, OCH_2Ph), 6.24 (2 H, s, H-4 and 6), and 7.28—7.50 (5 H, m, Ph); *m/e* 274 (M^+) (Found: C, 70.35; H, 6.45. $C_{16}H_{18}O_4$ requires C, 70.05; H, 6.61%).

Friedel–Crafts Reaction of Compound (6b) *with* 3,4-*Methylenedioxyphenylacetyl Chloride*.—The Friedel–Crafts reaction of compound (6b) was carried out in the same manner as described for compound (5). In this case, caution was taken in order to avoid the hydrolysis of one of the methoxyl groups. After completion of the reaction, ether was decanted out from the precipitated oily material and the latter, after being washed with ether, was treated for 1 h with 1% aqueous hydrochloric acid (20 ml) at 0 °C. The product was then isolated as before and purified by chromatography over silica gel. Elution with hexane–benzene (1 : 1) gave the *phenylbenzyl ketone* (2c) as an oil (yield, 45%), δ 3.80 (3 H, s, OMe), 3.89 (3 H, s, OMe), 3.93 (3 H, s, 2-OMe), 4.23 (2 H, s, $COCH_2Ph$), 5.92 (2 H, s, OCH_2O), 6.72 (3 H, m, H-2′,5′, and 6′), 6.73 (1 H, s, H-5), and 13.59 (1 H, s, CO • • • HO); *m/e* 346 (8) (M^+), 211 (66), and 135 (15) (Found: C, 62.55; H, 5.55. $C_{18}H_{18}O_7$ requires C, 62.42; H, 5.24%).

Synthesis of 3′,4′-*Methylenedioxy*-5,6,7-*trimethoxyisoflavone* (1b).—Ring closure of compound (2c) was effected by the same way as described for compound (2b). The crude product was purified by chromatography over silica gel and elution with benzene yielded the *isoflavone* (1b), which after recrystallisation from acetone had m.p. 179 °C (yield, 61%) (Found: C, 63.8; H, 4.6; O, 31.25. $C_{19}H_{16}O_7$ requires C, 64.04; H, 4.53; O, 31.43%). The u.v., i.r., ^1H n.m.r., and mass spectra of this compound were identical with those of odoratine. A mixed m.p. determination also showed no depression.

Ethylation of 2,5-*Dihydroxy*-1,3-*dimethoxybenzene* (4) *with Diethyl Sulphate and Alkali*.—Under an atmosphere of nitrogen, compound (4) (50 g) was dissolved in a solution of sodium hydroxide (50 g) in water (350 ml) and treated with diethyl sulphate (46 g) in the same manner as for the methylation. After the reaction, water (500 ml) was added at 0 °C, whereupon an oily material separated out. This was removed by means of a separating funnel from the aqueous alkaline solution. The latter was then neutralised with sulphuric acid and the separated oily product was chromatographed over silica gel. The chloroform eluate fraction afforded compound (6c) (30 g), which after crystallisation from chloroform–hexane (6 : 4) showed m.p. 112 °C, *m/e* 198 (M^+). The less-polar fraction was obtained in a

small amount by elution with benzene–chloroform (1 : 1), which was rechromatographed over silica gel. Elution with benzene yielded pure 1,3-dimethoxy-5-ethoxy-2-hydroxybenzene, m.p. 36—38 °C [from benzene–hexane (6 : 4)] (yield, 1%), *m/e* 198 (M^+).

5-Benzyloxy-1,3-dimethoxy-2-ethoxybenzene (6d).—The benzylation of compound (6c) was carried out by the same way as described for compound (6a). The crude product was purified by chromatography over silica gel. Elution with chloroform yielded the *benzyl ether* (6d), which after recrystallisation from hexane had m.p. 48 °C (yield, 69%); *m/e* 288 (M^+); δ 1.30 (3 H, t, *J* 7 Hz, OCH_2CH_3), 3.73 (6 H, s, 2 OMe), 3.91 (2 H, q, *J* 7 Hz, OCH_2CH_3), 4.90 (2 H, s, OCH_2Ph), 6.10 (2 H, s, H-4 and 6), and 7.25 (5 H, m, H-2′,3′,4′,5′, and 6′).

Friedel–Crafts Reaction of Compound (6d) *with 3,4-Methylenedioxyphenylacetyl Chloride*.—The Friedel–Crafts reaction of compound (6d) was carried out under the same condition as described for compound (6b). The crude product was chromatographed over silica gel and elution with benzene yielded the *phenylbenzyl ketone* (2d) as an oil (yield, 56%); δ 1.37 (3 H, t, *J* 7 Hz, OCH_2CH_3), 3.88 (3 H, s, 4-OMe), 3.97 (2 H, q, *J* 7 Hz, OCH_2CH_3), 4.01 (3 H, s, 2-OMe), 4.30 (2 H, s, $COCH_2Ph$), 5.95 (2 H, s, OCH_2O), 6.26 (1 H, s, H-5), 6.76 (3 H, m, H-2′,5′, and 6′), 13.18 (1 H, s, CO • • • HO); *m/e* 360 (14) (M^+), 225 (100), 197 (11), and 135 (16).

Synthesis of 5,7-Dimethoxy-6-ethoxy-3′,4′-methylenedioxyisoflavone (1f).—Ring closure of compound (2d) using ethyl formate and sodium was carried out by the same way as described for compound (2b). The crude product obtained was purified by chromatography over silica gel and elution with benzene–chloroform (9 : 1) gave the *isoflavone* (1f), which after recrystallisation from acetone showed m.p. 163 °C (yield 68%); $\lambda_{max.}$ 207 (log ε 4.32), 264 (4.22), and 292sh nm (4.00); $\nu_{max.}$ 1 645 (γ-pyrone CO), 1 620, 1 600, and 1 510 cm^{-1} (aromatic C=C); δ 1.40 (3 H, t, *J* 7 Hz, OCH_2CH_3), 3.95 (3 H, s, 7-OMe), 3.98 (3 H, s, 5-OMe), 4.13 (2 H, q, *J* 7 Hz, OCH_2CH_3), 6.00 (2 H, s, OCH_2O), 6.70 (1 H, s, H-8), 6.85 (1 H, d, $J_{5',6'}$ 8 Hz, H-5′), 7.01 (1 H, d, $J_{6'5'}$ 8 Hz, H-6′), 7.15 (1 H, m, H-2′), and 7.81 (1 H, s, H-2); *m/e* 370 (24) (M^+), 355 (8), 341 (100), 225 (5), 170 (6), 167 (5), 157 (6), 156 (21), 149 (8), 147 (7), 146 (16), and 145 (8) (Found: C, 64.65; H, 4.75; O, 30.05. $C_{20}H_{18}O_7$ requires C, 64.86; H, 4.90; O, 30.24%). The i.r. spectrum of this compound was different from that of the *O*-ethyl derivative of dipteryxine. A mixed m.p. determination also showed a depression.

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