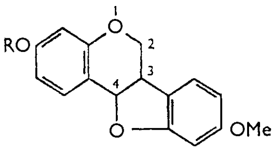
185. *A Synthesis of Demethylhomopterocarpin.*

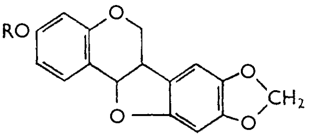
By Wesley Cocker, T. B. H. McMurry, and P. A. Staniland.

Demethylhomopterocarpin (I; R = H) has been synthesised and shown to be identical with an extractive from *Andira inermis*.

In an earlier Paper,[1] extractives from the West Indian hardwood, *Andira inermis* (Wright) H. B. K. were described. One of these, m. p. 112—113°, $[\alpha]_D^{20}$ −229·5°, showed ultraviolet absorption characteristics similar to those of homopterocarpin (I; R = Me) and demethylpterocarpin (II; R = H). We have now synthesised the racemic form of demethylhomopterocarpin (I; R = H) and shown it to be identical in gross structure with the extractive. Further, the naturally occurring isoflavonoid affords homopterocarpin (I; R = Me) on methylation.



(I)



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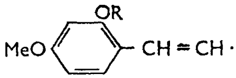

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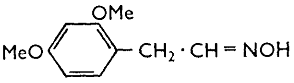

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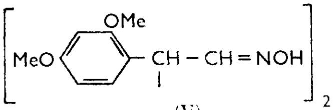

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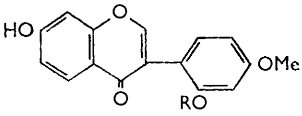

(VI)

The synthetic product (I; R = H) had m. p. 194—195°, some 80° higher than that of the optically active form, but its ultraviolet spectrum was in close agreement with that of the naturally occurring material (see Experimental section). The infrared spectra in chloroform of the two forms were identical, but in Nujol and potassium bromide, whilst being similar, were not identical. These are characteristics of a racemic compound and one of its active components. Racemic compounds usually have higher melting points than their components and in the solid state have different infrared spectra. In solution, racemic compounds dissociate and their spectra and those of their components become identical. The acetate of our synthetic demethylhomopterocarpin melted 45° lower than the acetate of the naturally occurring isoflavonoid but the two acetates showed identical ultraviolet and infrared spectra. The synthetic acetate thus behaves as a racemic mixture.

The natural and synthetic phenols and acetates had identical R_F values and mixtures of them were inseparable by chromatography.

Only one racemate of demethylhomopterocarpin is possible, since strain forbids *trans*-fusion at carbons 3 and 4. The naturally occurring isoflavonoid has the β-H configuration at these centres.[2]

The synthesis was carried out as follows. 2,4-Dimethoxybenzaldehyde[3] was condensed with nitromethane in presence of methylamine hydrochloride and sodium carbonate,[4] giving the nitrostyrene (III; R = Me).[5] This was reduced over palladised charcoal to 2,4-dimethoxyphenylacetaldoxime (IV),[6] which on dehydration gave 2,4-dimethoxybenzyl cyanide. The overall yield of cyanide was about 20%. Almost quantitative conversion

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[1] Cocker, Dahl, Dempsey, and McMurry, *J.*, 1962, 4906.
[2] Suginome and Iwadare, *Experientia*, 1962, **18**, 163.
[3] Cram, *J. Amer. Chem. Soc.*, 1948, **70**, 4240.
[4] Robinson and Sugasawa, *J.*, 1931, 3163.
[5] Rao, Srikantia, and Iyengar, *Helv. Chim. Acta*, 1929, **12**, 581.
[6] Reichert and Koch, *Arch. Pharm.*, 1935, **273**, 265.

of nitrostyrene to the oxime has been claimed,[6] but we could not attain these yields. In our hands the azlactone method [7] gave about 17% yield of cyanide.

A by-product of the hydrogenation of 2,4-dimethoxy-ω-nitrostyrene (III; R = Me) was α,α'-bis-(2,4-dimethoxyphenyl)succindialdoxime (V),[8] which on dehydration gave α,α'-bis-(2,4-dimethoxyphenyl)succindicyanide, m. p. 210—211°. This was hydrolysed to α,α'-bis-(2,4-dimethoxyphenyl)succinic acid, which readily gave an anhydride.

In an experiment designed to improve the yield of 2,4-dimethoxybenzyl cyanide, the crude product obtained from the hydrogenation of (III; R = Me) was dehydrated. Chromatography of the product gave a second dicyanide, m. p. 196—198° whose infrared spectrum was very similar to that of the higher-melting dicyanide. The lower-melting compound was much more soluble in organic solvents, but we found it difficult to hydrolyse and were unable to equilibrate it with the higher-melting form. Nevertheless, we believe that the latter is the *meso*-form and the former, the racemic form of the dicyanide.

7-Hydroxy-2',4'-dimethoxyisoflavone (VI; R = Me) was prepared by the method of Baker *et al.*,[9] the necessary ketone being obtained by condensation of 2,4-dimethoxybenzyl cyanide with resorcinol. The isoflavone was preferentially demethylated at the 2'-position with aluminium chloride [10] giving 2',7-dihydroxy-4'-methoxyisoflavone (VI; R = H). The latter was then reduced with borohydride [11] directly, giving demethylhomopterocarpin (I; R = H).

In another approach to the required isoflavone, 2-benzyloxy-4-methoxy-ω-nitrostyrene [12] was prepared from 2-benzyloxy-4-methoxybenzaldehyde. The nitrostyrene was reduced to 2-benzyloxy-4-methoxyphenethylamine, characterised as its picrate, whose melting point differed from that quoted in the literature.[12]

EXPERIMENTAL

Ultraviolet spectra refer to ethanol solutions and infrared spectra to Nujol mulls, unless otherwise stated.

2,4-Dimethoxybenzyl Cyanide.—2,4-Dimethoxybenzaldehyde [3] (156 g.) was stirred at room temperature in ethanol (500 c.c.) with nitromethane (47 g.), anhydrous sodium carbonate [4] (7 g.), and methylamine hydrochloride (7 g.). After 6 hr. the yellow crystalline mass was collected, giving 2,4-dimethoxy-ω-nitrostyrene (80 g.) as yellow needles, m. p. 104° (from ethanol) (lit.,[5] 104°), $\nu_{max.}$ 1623 (Ar–C=C), 1600, 1572, 1543 (C=C–NO_2) 1488, and 1025 cm.$^{-1}$ (Found: C, 57·3; H, 5·3. Calc. for $C_{10}H_{11}NO_4$: C, 57·4; H, 5·3%). More nitrostyrene (75 g., total 82%) was obtained from the mother-liquors on longer standing.

The nitrostyrene (20 g.) was shaken for 4 hr. in an atmosphere of hydrogen with ethyl acetate (65 c.c.), pyridine (15 c.c.), and palladised charcoal (2 g.). The product, an oil, was stirred with hot ethyl acetate (40 c.c.) giving meso-*α,α'-bis-(2,4-dimethoxyphenyl)succindialdoxime* (2 g.) as prisms, m. p. 226—227° (from ethanol), $\nu_{max.}$ 3279 and 1613 (=N–OH), 1587 and 1504 (Ar), 1026 (OMe), and 945 cm.$^{-1}$ (N–O) (Found: C, 62·1; H, 6·5; OMe, 32·0. $C_{20}H_{24}N_2O_6$ requires C, 61·8; H, 6·2; 4OMe, 32·0%). It gave a green ferric chloride reaction.

The mother-liquors were cooled, when 2,4-dimethoxyphenylacetaldoxime (8 g.) was deposited as prisms, m. p. 115—116° (lit.,[6] 119°), $\nu_{max.}$ 3195 (=N–OH), 1672 (C=N), 1623, 1592, 1508, and 1031 cm.$^{-1}$ (OMe) (Found: C, 61·6; H, 6·6; OMe, 32·3. Calc. for $C_{10}H_{13}NO_3$: C, 61·5; H, 6·7; 2OMe, 31·8%). A mixture of this compound (20 g.), acetic anhydride (60 c.c.), and sodium acetate (6 g.) was heated at 100° for 0·5 hr. and then refluxed for 10 min. The required 2,4-dimethoxybenzyl cyanide (14 g.) was obtained as colourless needles, m. p. 76° (from ethanol) (lit.,[6] 76°), $\nu_{max.}$ 2247 (CN), 1621, 1595, 1504, and 1027 cm.$^{-1}$ (Found: C, 67·2; H, 6·0. Calc. for $C_{10}H_{11}NO_2$: C, 67·8; H, 6·3%).

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[7] Mitter and Maitra, *J. Indian Chem. Soc.*, 1936, **13**, 236.

[8] Sonn and Schellenberg, *Ber.*, 1917, **50**, 1513.

[9] Baker, Chadderton, Harborne, and Ollis, *J.*, 1953, 1852.

[10] Aghormurthy, Kukla, and Seshadri, *J. Indian Chem. Soc.*, 1961, **38**, 914.

[11] Aghormurthy, Kukla, and Seshadri, *Current Sci.*, 1961, **30**, 218.

[12] Merchant and Mountwala, *J. Org. Chem.*, 1958, **23**, 1774.

meso-α,α′-*Bis*-(2,4-*dimethoxyphenyl*)*succindicyanide*.—The foregoing dioxime (4 g.) was refluxed for 1 hr. with acetic anhydride (20 c.c.) and sodium acetate (4 g.) giving the meso-*dicyanide* (2·5 g.) as a brown solid which crystallised from ethyl acetate as colourless microprisms, m. p. 210—211°, $\nu_{max.}$ 2232 (CN), 1603, 1575, 1497, and 1026 cm.$^{-1}$ (Found: C, 68·4; H, 5·9; N, 8·0. $C_{20}H_{20}N_2O_4$ requires C, 68·2; H, 5·7; N, 7·95%).

meso-α,α′-*Bis*-(2,4-*dimethoxyphenyl*)*succinic Acid*.—The cyanide (0·9 g.) was refluxed for 1·5 hr. with glacial acetic acid (6·6 c.c.), sulphuric acid (6·6 c.c.), and water (6·6 c.c.), and poured into water. The product was collected, dissolved in 5% sodium hydroxide, filtered, and washed thrice with chloroform. The alkaline solution was acidified giving the required *acid* (0·7 g.) which crystallised from dioxan as micro needles, m. p. 245—248° (decomp.), $\nu_{max.}$ 2597 and 1704 cm.$^{-1}$ (CO_2H) (Found: C, 61·15; H, 5·5%; Equiv., 195. $C_{20}H_{22}O_8$ requires C, 61·5; H, 5·7%; Equiv., 195). Its *anhydride* (1·0 g.) was obtained as prisms, m. p. 151—152° (from ethyl acetate–light petroleum), $\nu_{max.}$ 1866 and 1780 (anhydride), 1613, 1506, and 1031 cm.$^{-1}$, when the acid (1·5 g.) was heated for 2 hr. at 100° with acetic anhydride (10 c.c.) (Found: C, 65·1; H, 5·5. $C_{20}H_{20}O_7$ requires C, 64·5; H, 5·4%).

Racemic α,α′-*Bis*-(2,4-*dimethoxyphenyl*)*succindicyanide*.—The crude oil obtained from the hydrogenation of 2,4-dimethoxy-ω-nitrostyrene (10 g.) was refluxed for 1 hr. with acetic anhydride (20 c.c.). Removal of acetic anhydride *in vacuo* gave a dark gum which was eluted from a column of neutral alumina with ligroin–benzene (20 : 80). 2,4-Dimethoxybenzyl cyanide (2 g.) was first eluted. Later fractions afforded the *racemic dicyanide* (0·5 g.) which crystallised as needles, m. p. 196—198° (from ethyl acetate), $\nu_{max.}$ 2262, 1613, 1582, and 1023 cm.$^{-1}$ (Found: C, 68·1; H, 5·85; N, 8·2%).

2′,4′-*Dihydroxyphenyl* 2,4-*Dimethoxybenzyl Ketone*.—2,4-Dimethoxybenzyl cyanide (10 g.) was set aside for 48 hr. at 0° with resorcinol (20 g.) in dry ether (200 c.c.) previously saturated with hydrogen chloride. The ether was decanted, the residue was collected and heated at 100° for 6 hr. with water (30 c.c.). The product was crystallised from dilute ethanol giving the ketone as colourless plates (6 g.), m. p. 154° (lit.,[13] 158—159°), $\nu_{max.}$ 3257, 1631 (Ar–C=O), 1600, 1499, and 1034 cm.$^{-1}$ (Found: C, 67·1; H, 5·8; OMe, 20·5. Calc. for $C_{16}H_{16}O_5$: C, 66·7; H, 5·6; 2OMe, 21·4%).

2-*Ethoxycarbonyl*-7-*hydroxy*-2′,4′-*dimethoxyisoflavone*.—The preceding compound (3 g.) was set aside at 15° for 60 hr. with freshly distilled ethoxalyl chloride [9] (4·4 g.) and pyridine (35 c.c.). The red mixture was poured on to ice and the product was collected in chloroform, from which, after washing with 10% hydrochloric acid, the *isoflavone* (1·8 g.) was obtained as prisms, m. p. 228—229° (from aqueous ethanol), $\nu_{max.}$ 3226 (OH), 1739 (CO_2Et), 1631 (pyrone C=O), 1575, 1508, and 1036 cm.$^{-1}$ (Found: C, 64·7; H, 5·1. $C_{20}H_{18}O_7$ requires C, 64·9; H, 4·9%).

7-*Hydroxy*-2′,4′-*dimethoxyisoflavone*.—The ester (1 g.) was heated at 100° for 4 hr. in acetone (20 c.c.) with 10% sodium carbonate (20 c.c.). Acetone was removed and the mixture acidified, giving 7-hydroxy-2′,4′-dimethoxyisoflavone-2-carboxylic acid (0·7 g.), m. p. 251—255° (decomp.), $\nu_{max.}$ 3067, 1712 (CO_2H), 1631, 1592, 1506, and 1033 cm.$^{-1}$. The acid was heated for 3 min. at 270° and then sublimed at 270°/0·5 mm. giving 7-*hydroxy*-2′,4′-*dimethoxyisoflavone* (0·5 g.). For analysis a specimen was washed with cold methanol and resublimed, m. p. 265—267°, $\lambda_{max.}$ 2130 and 2490 Å (log ε 4·01 and 4·44), $\nu_{max.}$ 3195, 1631, 1575, 1497, and 1028 cm.$^{-1}$ (Found: C, 68·5; H, 4·9; OMe, 20·4. $C_{17}H_{14}O_5$ requires C, 68·45; H, 4·7; 2OMe, 20·8%). It gave no ferric reaction.

2′,7-*Dihydroxy*-4′-*methoxyisoflavone* (VI; R = H).—The preceding compound (1·2 g.) was refluxed for 12 hr. with aluminium chloride (4 g.) in methyl cyanide [10] (30 c.c.). The solvent was removed, the residue was treated with cold 10% hydrochloric acid and extracted with chloroform. The extract was washed with water and dried giving the *isoflavone* (0·8 g.) as needles, m. p. 212—215°, (from aqueous ethanol), $\lambda_{max.}$ 2170, 2500, and 2880 Å (log ε 4·2, 4·41, and 4·52), $\nu_{max.}$ 3311, 1631, 1575, 1502, and 1028 cm.$^{-1}$ (Found: C, 66·9; H, 4·3; OMe, 11·4. $C_{16}H_{12}O_5$ requires C, 67·6; H, 4·3; 1OMe, 10·9%). It gave no ferric chloride reaction.

Demethylhomopterocarpin (I; R = H).—A solution of sodium borohydride [11] (0·7 g.) in absolute ethanol (15 c.c.) was added dropwise to the isoflavone (VI; R = H) (0·6 g.) in tetrahydrofuran (15 c.c.), and the mixture was set aside for 60 hr. Acetone (10 c.c.) was added to decompose excess of borohydride, solvents were removed, and 10% hydrochloric acid was added to the residue, which was extracted with chloroform. Thin-layer chromatography on silica gel showed the presence of unchanged isoflavone. The product was therefore eluted from

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[13] Sehgal and Seshadri, *Proc. Indian Acad. Sci.*, 1955, **42**, *A*, 36.

a column of silica gel with benzene giving the required *racemic demethylhomopterocarpin* as the first fraction. It crystallised from ethyl acetate–light petroleum (b. p. 40—60°) as prisms (0·18 g.), m. p. 194—195° (Found: C, 71·2; H, 5·5. $C_{16}H_{14}O_4$ requires C, 71·1; H, 5·2%), $\lambda_{max.}$ 2065 (2280), 2820, 2870, and 3100 Å [log ε 4·80, (4·14), 3·92, 3·96, and 2·01], $\nu_{max.}$ ($CHCl_3$), 3240 (OH), 1618, 1595, and 1026 cm.$^{-1}$, $\nu_{max.}$ (KBr) 3333, 1620, 1592, and 1026 cm.$^{-1}$, $\nu_{max.}$ 3333, 1618, 1590, and 1027 cm.$^{-1}$. The " natural " specimen had $\lambda_{max.}$ 2070 (2275), 2820, 2870, and 3100 Å [log ε 4·86 (4·23), 3·97, 4·01, and 3·38], $\nu_{max.}$ ($CHCl_3$) 3240, 1618, 1595, and 1026 cm.$^{-1}$, $\nu_{max.}$ (KBr) 3333, 1621, 1595, and 1026 cm.$^{-1}$, $\nu_{max.}$ 3333, 1613, 1587, and 1018 cm.$^{-1}$.

Demethylhomopterocarpin Acetate.—The phenol (0·1 g.) was heated for 2 hr. at 100° with acetic anhydride (0·4 c.c.) and pyridine (2 c.c.) giving an oil which solidified on trituration with ether and crystallised from ethanol as needles, m. p. 105—106° (Found: C, 67·8; H, 5·3. $C_{18}H_{16}O_5,\frac{1}{2}H_2O$ requires C, 67·3; H, 5·3%), $\lambda_{max.}$ 2060, (2260), 2855, 3200 Å [log ε 4·85, (4·21), 4·06, and 3·03] $\nu_{max.}$ ($CHCl_3$), 1754 (ester), 1618, 1600, and 1007 cm.$^{-1}$, $\nu_{max.}$ 1742, 1620, 1595, and 1022 cm.$^{-1}$. Acetate from " natural " specimen had $\lambda_{max.}$ 2080, (2260), 2860, and 3100 Å [log ε 4·39, (3·96), 3·72, and 3·19], $\nu_{max.}$ ($CHCl_3$) 1754, 1618, 1600, and 1009 cm.$^{-1}$, $\nu_{max.}$ 1757, 1623, 1592, and 1021 cm.$^{-1}$.

Methylation of " Natural " Demethylhomopterocarpin.—This compound (20 mg.) was refluxed for 2·5 hr. with methyl iodide (0·1 c.c.), potassium carbonate (0·2 g.), and acetone (7 c.c.). Solvent was removed, the residue was extracted with chloroform, which was washed with 5% sodium hydroxide and then with water, giving an oil. This was dissolved in hot ethyl acetate–light petroleum from which homopterocarpin was obtained as needles, (10 mg.), m. p. 82—83° undepressed by an authentic specimen, m. p. 83—84° (lit.,[14] 87°). The infrared spectra (Nujol) of the two specimens were identical, $\nu_{max.}$ 1616, 1577, 1488, and 1027 cm.$^{-1}$.

Chromatographic Examination of Synthetic and " Natural " Demethylhomopterocarpin and Derivatives.—Solutions of these compounds in ethyl acetate were spotted on silica gel G (Merck) and developed with the solvents shown.

Compound	Solvent	R_F
Natural phenol (A)	Benzene–ether (50 : 50)	0·76
Synthetic phenol (B)	,,	0·76
Mixture of phenols	,,	0·76
Acetate of (A)	Benzene–ether (90 : 10)	0·72
,, of (B)	,,	0·72
Mixture of acetates	,,	0·72
Methyl ether of (A)	Benzene–light petroleum (80 : 20)	0·39
Homopterocarpin	,,	0·39
Mixture of methyl ethers	,,	0·39

2-*Benzyloxy*-4-*methoxy*-ω-*nitrostyrene* (III; R = $PhCH_2$).—2-Benzyloxy-4-methoxybenzaldehyde [15] (2·5 g.) was stirred at 15° for 12 hr. with nitromethane (0·7 g.), methylamine hydrochloride (0·1 g.), sodium carbonate (0·1 g.) and ethanol (10 c.c.). The *nitrostyrene* (2·4 g., 80%) crystallised as bright yellow needles, m. p. 115—116° (from ethyl acetate) (lit.,[12] oil, but stated to be crude), $\lambda_{max.}$ 3775 and 2540 Å (log ε 3·24 and 3·0), $\nu_{max.}$ 1610 and 1500 (Ar), 1513 and 1321 ($C=C-NO_2$), and 1028 cm.$^{-1}$ (OMe) (Found: C, 67·7; H, 5·4. $C_{16}H_{15}NO_4$ requires C, 67·4; H, 5·3%).

2-*Benzyloxy*-4-*methoxyphenethylamine picrate* was prepared from (III; R = $PhCH_2$) by the method of Merchant and Mountwala.[12] It consisted of orange needles, m. p. 177—178° (lit.,[12] 143—145°) (Found: C, 54·8; H, 4·7. $C_{22}H_{22}N_4O_9$ requires C, 54·3; H, 4·6%).

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[14] McGookin, Robertson, and Whalley, *J.*, 1940, 787.

[15] Sonn and Patschke, *Ber.*, 1925, **58**, 1698.