Proc. Indian Acad. Sci. (Chem. Sci.), Vol. 100, No. 1, February 1988, pp. 45–52.
© Printed in India.

Synthesis of natural (±)-dihydrocladrin, (±)-homoferreirin and related isoflavanones

AMOLAK C JAIN*, OM D TYAGI and ASHOK K PRASAD
Department of Chemistry, University of Delhi, Delhi 110 007, India

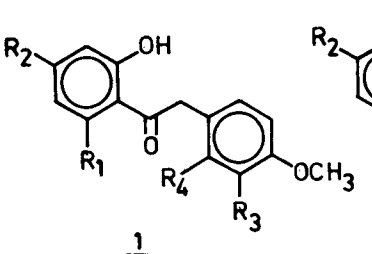
MS received 11 August 1987; revised 26 November 1987

Abstract. Two naturally occurring isoflavanones, viz. dihydrocladrin and homoferreirin, and related compounds, di-O-methylhomoferreirin and 7-O-methylsativanone, have been synthesized in racemic forms from the corresponding desoxybenzoins using the ethoxymethyl chloride method from the literature.

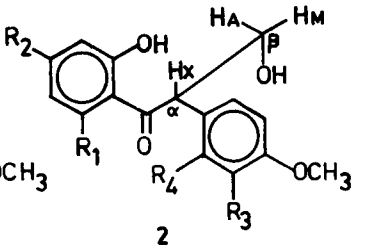
Keywords. α-Hydroxymethyldesoxybenzoins; ethoxymethoxyisoflavanones.

1. Introduction

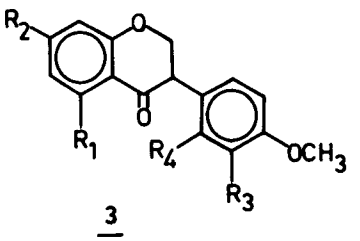
Nearly forty isoflavanones are known so far to occur in different plants (Dewick 1982; Ingham *et al* 1983). One of them is dihydrocladrin (or 7-hydroxy-3′,4′-dimethoxyisoflavanone, 3a) isolated recently by Ohashi *et al* (1982) from the heartwood of *Cladrastis shikokiana* (Leguminosae; Lotoideae), infected by a white-rot fungus, *Lenzites betulina* (Polyporaceae). The isolation of this isoflavanone is significant because the derived pterocarpans show fungitoxic activity. Another



1



2



3

(a) $R_1 = R_4 = H$, $R_2 = OH$, $R = OCH_3$
(b) $R_1 = R_4 = H$, $R_2 = OCH_2OEt$, $R = OCH_3$
(c) $R_1 = R_2 = OH$, $R_3 = H$, $R_4 = OCH_3$
(d) $R_1 = R_2 = OCH_2OEt$, $R_3 = H$, $R_4 = OCH_3$
(e) $R_1 = R_2 = R_4 = OCH_3$, $R_3 = H$
(f) $R_1 = R_3 = H$, $R_2 = R_4 = OCH_3$

*To whom all correspondence should be addressed.

compound, homoferreirin (3c) is the earliest known natural isoflavanone occurring in Ferreirea spectabilis (King *et al* 1952). The former isoflavanone (3a) was partially synthesized from natural cladrin by hydrogenation in the presence of platinic oxide (Ohashi *et al* 1982), and the latter was synthesized first by Neill (1953) and later by Grover and Makrandi (1978), albeit in very poor yields. The recently designed general synthesis of hydroxyisoflavanones (Jain and Sharma 1984, 1985; Jain and Mehta 1986) has now been adopted to synthesize them in good yields.

2. Results and discussion

All spectral data are presented in tables 1–3.

2.1 *Synthesis of dihydrocladrin (3a)*

2,4-Dihydroxy-3′,4′-dimethoxydesoxybenzoin (Spath and Schmidt 1929) (1a) when reacted with ethoxymethyl chloride in the presence of ignited K_2CO_3 and acetone gave 4-ethoxymethoxy-2-hydroxy-α-hydroxymethyldesoxybenzoin (2b) in 85.1% yield. It was identified by its ^{1}H-NMR spectrum which showed a ethoxymethyl group δ 1·17, *t*; 3·62, *q*; and 5·18, *s*) and a set of three double doublets (δ 4·12, 4·37 and 4·72) of the AMX pattern besides other signals of the parent compound. Cyclisation of the alcohol (2b) was accomplished with 2% aqueous ethanolic sodium carbonate in 74·5% yield. The resulting 7-ethoxymethoxy-3′,4′-dimethoxyisoflavanone (3b) on deprotection with 10% methanolic hydrogen chloride afforded 7-hydroxy-3′,4′-dimethoxyisoflavanone (3a) with properties identical to that of the natural sample (m.p., UV, NMR, and similar data on the acetate, Ohashi *et al* 1982).

2.2 *Synthesis of homoferreirin (3c), its dimethyl ether (3e) and 7-O-methylsativanone (3f)*

These isoflavanones have been synthesized from the ketones (1c, 1e and 1f). The ketone (1c) was α-hydroxymethylated with 3 mol of ethoxymethyl chloride, followed by cyclization of the resulting alcohol (2d) in the presence of a base and deprotection of 5,7-diethoxymethoxy-2′,4′-dimethoxyisoflavanone (3d). The ketones (1e) and (1f) were treated with one mole of ethoxymethyl chloride to give 2e and 2f respectively, and cyclized with a base when (3e) and (3f) were obtained in 75% and 63·8% yield, respectively.

3. Experimental

All melting points are uncorrected. The following spectrometers were used for spectral measurements; UV Shimadzu 260; IR Shimadzu 435; NMR 90 MHz Perkin–Elmer R-32 or 200 MHz JNM FX-200 Jeol FT NMR. UV data were taken in MeOH; λ max values are in nm and values in parentheses are log ϵ, IR values are recorded in cm^{-1} using nujol film or KBr disc, NMR data were recorded in different solvents using TMS as an internal standard, chemical shifts are reported in δ values (ppm) and *J* values in Hz. Silica gel G was used for TLC and silica gel

Table 1.

Compd. No.	m.p	R_f	IR Absorption peaks of characteristics grps. (in cm^{-1})	Absorption maxima nm.(log ϵ)in the UV absorption spectra	C/H Analysis (%) Found C	Found H	Calculated C	Calculated H	Molecular formula
2 b	Yellow oil	0·40 Sol–A	3490, 1625, 1590 and 1505	207, 223, 272 and 313	–	–	–	–	–
3 b	101–02°	0·55 Sol–A	1662 and 1605	206 (4·71), 226 (4·55) 270 (4·45) and 310 (4·09)	67·2	6·5	67·0	6·2	$C_{20}H_{22}O_6$
3 a	100–91°	0·40 Sol–B	3425, 1658 and 1580	274 (4·25) and 314 (4·10)	68·2	5·0	68·0	5·4	$C_{17}H_{16}O_5$
2 d	Viscous	0·50 Sol–A	2900, 1640(sh), 1600 and 1500	202, 220, 282 and 330(sh)	–	–	–	–	–
3 d	Viscous	0·60 Sol–A	1670, 1600 and 1500	218, 278	–	–	–	–	–
3 c	168–69°	0·30 Sol–B	3350, 2900, 1670(sh) 1600(br) and 1500	202 (4·50), 224 (4·34), 284 (4·29) and 330(sh) (3·58)	66·6	4·9	66·5	4·8	$C_{17}H_{16}O_6$
2 e	91–92°	0·50 Sol–A	2900, 1645(sh), 1600 and 1500	206 (4·67), 224 (4·51), and 282 (4·42)	63·5	5·2	63·0	5·0	$C_{19}H_{22}O_7$
3 e	164–65°	0·50 Sol–B	1675, 1600, 1570 and 1500	204 (4·61), 220 (4·51), and 282 (4·42)	66·4	5·9	66·3	5·8	$C_{19}H_{20}O_6$
2 f	97–98°	0·55 Sol–A	2900, 1645(sh), 1610 and 1500	207 (4·47), 226(sh) (4·31), 272 (4·28) and 314 (4·04)	63·4	6·4	63·9	6·0	$C_{18}H_{20}O_6$
3 f	109–10°	0·40 Sol–B	1670, 1585 and 1500	204 (4·48), 224 (4·41), 272 (4·28) and 306 (3·90)	68·8	5·8	69·0	5·7	$C_{18}H_{18}O_5$

Table 2. Assignments of chemical shifts (δ) of the protons in the NMR spectra (J in C/s).

Compd. No.	alc. –OH	2–H	3–H	4–H	5–H	6–H	7–H	8–H	2′–H	3′–H	4′–H	5′–H	6′–H	–OCH_3	H_A	H_M	H_X	–O.CH_2.O–	CH_3–CH_2	Chelated –OH
2b	2·96 (bs)	–	6·57 d,J=2·5	–	6·46 (m)	7·76 dJ=9	–	–	6·85 (s)	–	–	6·85 (s)	6·85 (s)	3·81 & 3·85	4·14 (dd) JAM=11·2; JAX=4.8	4·37 (dd) JMX=8·2;	4·72 (dd)	5·18 (s)	1·17(t) & 3·62(q)	12·94 (s)
3b	–	4·60 d,J=7	4·10 q	–	7·85 d,J=9	6·66 m	–	6·66 m	6·81 s	–	–	6·81 s	6·81 s	3·81 s	–	–	–	5·22 s	1·20 (t) & 3·65(q)	– –
3a	–	4·52 & 4·56 d each J=6,9	3·90 dd J=6,9	–	7·62 d,J=9	6·46 dd J=2,9	–	6·30 d,J=2	6·82 d,J=2	–	–	6·85 d,J=9	6·75 dd J=2,9	3·63 s	–	–	–	–	–	–
2d	2·86 bs	–	6·42 bs	–	6·42 bs	–	–	–	–	6·24 m	–	6·24 m	6·80 d,J=10	3·70 m	3·70 m	4·02 dd JAM=11·2; JMX=8·2; JAX=4.8	4·98 dd	5·12 & 5·24 2s	1·18(t) 3·24 & 3·46 q each	13·24 s
3d	–	4·46 m	4·12 m	–	–	6·37 m	–	6·37 m	–	6·37 m	–	6·37 m	6·98 d,J=10	3·70 m	–	–	–	5·21,5·26 s each	1·12,(t) 3·70(m)	–
3c	–	4·46 m	4·24 m	–	–	5·90 s	–	5·92 s	–	6·50 m	–	6·50 m	7·02 d,J=10	3·77 bs	–	–	–	–	–	12·28 s
2e	2·58 bs	–	6·02 s	–	5·70 s	–	–	–	–	6·34 m	–	6·34 m	6·78 d,J=10	3·65 m	3·65 m	4·00 dd JAM=11·2; JMX=8·2; JAX=4.8	5·20 dd	–	–	13·68 s
3e	–	4·52 m	4·18 m	–	–	6·14 s	–	6·19 s	–	6·52 m	–	6·52 m	7·04 d,J=10	3·80 m	–	–	–	–	–	–
2f	2·58 bs	–	6·34 m	–	6·34 m	7·54 d,J=10	–	–	–	6·34 m	–	6·34 m	6·92 d,J=10	3·76 m	3·76 m	4·14 dd JAM=11·2; JMX=8·2; JAX=4.8	5·04 dd	–	–	12·64 s
3f	–	4·54 m	4·16 m	–	7·80 d,J=10	6·54 m	–	6·54 m	–	6·54 m	–	6·54 m	6·98 d,J=10	3·80 m	–	–	–	–	–	–

Table 3. Assignments of chemical shifts (δ) of the protons in the ^{13}C–NMR spectra of compounds.

Compd. No.	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8	C_9	C_{10}	$C_{1'}$	$C_{2'}$	$C_{3'}$	$C_{4'}$	$C_{5'}$	$C_{6'}$	C_α	C_β	OCH_2O	CH_3–	CH_2–	C=O	OCH_3
2d	118·70 s	160·48 s	94·51 d	167·33 s	97·26 d	157·80 s	–	–	–	–	106·96 s	159·95 s	98·94 d	164·00 s	104·10 d	128·73 d	53·69 d	63·60 t	92·77 & 93·64 2t	14·95 q	64·30 & 64·76 m	206·21 s	55·30 2q
3d	–	70·50 t	48·22 d	–	160·05 s	98·63 d	164·73 s	97·41 d	158·41 s	116·63 s	95·50 s	160·35 s	99·06 d	163·03 s	104·65 d	130·56 d	–	–	92·85 & 94·07 m	15·02 q	64·70 t	189·97 s	55·45 m
3c	–	70·70 t	46·94 d	–	161·15 s	96·70 d	166·50 s	95·40 d	151·02 s	116·20 s	104·10 s	164·10 s	99·42 d	165·20 s	105·40 d	131·17 d	–	–	–	–	–	197·63 s	55·20 & 55·70 2q

for column chromatography. Light petroleum used had a boiling range 60–80°C. R_f values are those recorded on TLC plates which were sprayed with 1% ethanolic ferric chloride for 10% aqueous H_2SO_4. The solvent systems used for TLC were: (A) benzene-ethyl acetate (19:1), (B) benzene-ethyl acetate (9:1).

3.1 *4-Ethoxymethoxy-2-hydroxy-α-hydroxymethyl-3',4'-dimethoxydesoxybenzoin (2b)*

A solution of 2,4-dihydroxy-3',4'-dimethoxydesoxybenzoin (Spath and Schmidt 1929) (1a, 1·44 g, 5 mmol) in dry acetone (100 ml) was treated with anhydrous K_2CO_3 (3·5 g, 25 mmol), followed by a solution of ethoxymethyl chloride (0·66 ml, 5 mmol) in dry acetone (15 ml). The resulting mixture was stirred until TLC showed full conversion of 1a into a product considered to be 4-ethoxymethoxy-2-hydroxy-3',4'-dimethoxydesoxybenzoin (45 min). A further amount of ethoxymethyl chloride (0·66 ml, 5 mmol) was added to the above reaction mixture and the solution warmed initially at 40–50° for 10–15 min and then at 60–70° until TLC showed almost complete conversion of the above. The reaction mixture was filtered hot and the filtrate concentrated at room temperature. The residue was treated with crushed ice, the oily product extracted with ether and the ether residue subjected to column chromatography. It was eluted first with petrol and then with petrol-ethyl acetate (49:1). The latter eluate afforded 2b as a viscous yellow oil (1·6 g, 85·1% yield) which gave violet green ferric reaction.

3.2 *7-Ethoxymethoxy-3',4'-dimethoxyisoflavanone (3b)*

The above α-hydroxymethyl derivative (2b, 1·128 g, 3 mmol) was refluxed with EtOH (20 ml) and 4% aqueous Na_2CO_3 (20 ml) for 40 min. Ethanol was distilled off *in vacuo* and the residue purified by column chromatography when 3b was obtained as a white solid (800 mg, 74·5% yield); It crystallized from benzene-petrol as colourless crystals.

3.3 *7-Hydroxy-3',4'-dimethoxyisoflavanone or dihydrocladrin (3a)*

A solution of the above isoflavanone (3b, 537 mg, 1·5 mmol) in MeOH (20 ml) was warmed slowly with 10% MeOH-HCl (20 ml) for 15 min. The solution was concentrated to half the bulk, cooled, treated with an equal amount of cold H_2O and left overnight in a refridgerator. The solid thus separated was collected and crystallized from MeOH when 3a was obtained as white needles (375 mg, 83·3% yield) (Ohashi *et al* 1982, m.p. 187–89°C). The acetate prepared by the Ac_2O-pyridine method crystallized from chloroform; m.p. 134–35°C (Ohashi *et al* 1982, m.p. 132–3°C); 90 MHz PMR(DMSO-d_6); 2·26(3H, *s*, $-O-COCH_3$), 3·72(6H, *s*, $2 \times -OCH_3$), 4·06(1H, *d*, *d*, $J = 6$ and 9, H–3), 4·68(2H, m, H–2), 6·74–6·88(5H, *m*, aromatic H), and 7·88(1H, *d*, $J = 9$, H–5). With regard to all the spectral data, both the above hydroxy compound and its acetate agreed with those of the natural sample and its acetate, respectively.

3.4 *4,6-Diethoxymethoxy-2-hydroxy-α-hydroxymethyl-2',4'-dimethoxydesoxybenzoin (2d)*

A solution of 2,4,6-trihydroxy-2',4'-dimethoxydesoxybenzoin (Neill 1953) (1c, 1·52 g, 5 mmol) in dry acetone (80 ml) was treated with anhydrous K_2CO_3 (2·76 g,

20 mmol) followed by addition of ethoxymethyl chloride (first 1·32 ml, 10 mmol) and later 0·66 ml (5 mmol). The product (2d) was obtained as a viscous oil (1·15 g, 51.1% yield) which gave a violet ferric reaction.

3.5 *5,7-Diethoxymethoxy-2',4'-dimethoxyisoflavanone (3a)*

The above α-hydroxymethyl derivative (2d) (1·0 g, 2·2 mmol) was refluxed with ethanol (20 ml) and 4% aqueous Na_2CO_3 (20 ml) for 1·5 h. The usual work-up of the reaction mixture afforded 3d as brown viscous oil (0·6 g, 66·7% yield).

3.6 *5,7-Dihydroxy-2',4'-dimethoxyisoflavanone (or homoferreirin) (3c)*

A solution of the above isoflavanone (3d, 0·5 g, 1·16 mmol) in methanol (20 ml) was warmed with 10% MeOH-HCl (20 ml) for 10 min. The product crystallized from EtOH to afford 3c as white plates (0·3 g, 81·9% yield) (King *et al* 1952, m.p. 169°C) which gave a violet ferric reaction.

3.7 *2-Hydroxy-α-hydroxymethyl-4,6,2',4'-tetramethoxy desoxybenzoin (2e)*

To a solution of 2-hydroxy-4,6,2',4'-tetramethoxydesoxybenzoin (Govindachari *et al* 1961) (1e, 1·66 g, 5 mmol) in dry acetone (80 ml), was added anhydrous K_2CO_3 (2·7 g, 20 mmol) and a solution of ethoxymethyl chloride (0·66 ml, 5 mmol) in dry acetone (10 ml). The reaction mixture was warmed initially at 40–50° and then at 60–70° for 1·5 h. The product was subjected to column chromatography. Elution of the column with petrol-ethyl acetate (19:1) afforded 2e which crystallized from ethyl acetate-petrol mixture as almost colourless plates (1·4 g, 77·8% yield) which gave a violet ferric reaction.

3.8 *5,7,2',4'-Tetramethoxyisoflavanone (di-O-methyl-homoferreirin) (3e)*

The above α-hydroxymethyl derivative (2e, 0·5 g, 1·38 mmol) was refluxed with 4% aqueous Na_2CO_3 and C_2H_5OH for 1 h. The product was purified by column chromatography and then crystallized from ethanol when 3e was obtained as a white solid (0·3 g, 75% yield) (King *et al* 1952, m.p. 165–66°C).

3.9 *2-Hydroxy-α-hydroxymethyl-4,2',4'-trimethoxydesoxy-benzoin (2f)*

A mixture of 2-hydroxy-4,2',4'-trimethoxydesoxybenzoin (Suginome 1958) (1f, 1·50 g, 5 mmol), dry acetone (100 ml), anhydrous K_2CO_3 (2·7 g, 20 mmol) and ethoxymethyl chloride (0·66 ml, 5 mmol) was refluxed. The product crystallized from petrol-benzene to afford 2f as colourless plates (1·4 g, 77·8% yield) which gave a violet ferric reaction.

3.10 *7,2',4'-Trimethoxyisoflavanone or 7-O-methyl-sativanone (3f)*

The above α-hydroxymethyldesoxybenzoin (2f, 0·5 g, 1·51 mmol) was refluxed with CH_3OH (15 ml) and 4% aqueous Na_2CO_3 (15 ml). The product obtained was crystallized from chloroform to afford 3f as light brown plates (0·3 g, 63·8% yield) (Anirudhan *et al* 1966, m.p. 111–12°C)

Acknowledgements

The authors express their sincere gratitude to the CSIR, New Delhi, for the award of fellowships to ODT and AKP.

References

Anirudhan C A, Whalley W D and Badran M M E 1966 *J. Chem. Soc. (C)* **64** 629
Dewick P M 1982 in *The flavonoids: advances in research* (eds) J B Harborne and T J Mabry (London, New York: Chapman and Hall) p. 635
Govindachari T R, Nagarajan K and Parthasarathy P C 1961 *Tetrahedron* **15** 129
Grover S K and Makrandi J K 1978 *Curr. Sci.* **47** 85
Ingham J L, Koskinen A and Lounasmaa M 1983 in *Progress in the chemistry of organic natural products* (eds) W Herz, H Grisebach and G W Kirby (Wien, New York: Springer–Verlag) vol. 43, p. 87
Jain A C and Mehta A (*nee* Sharma) 1986 *J. Chem. Soc., Perkin I* 215
Jain A C and Sharma A 1984 *Indian J. Chem.* **B23** 451
Jain A C and Sharma A 1985 *J. Chem. Soc., Chem. Commun.* 3380
King F E, Gruden M E and Neill K G 1952 *J. Chem. Soc.* 4580
Neill K G 1953 *J. Chem. Soc.* 3454
Ohashi H, Takeuchi H, Umemura S and Imamura H 1982 *Mokuzai Gokkaishi* **28** 463
Spath E and Schmidt O 1929 *Mh Chem.* **53** 454
Suginome H 1958 *J Org. Chem.* **23** 1044