BIOORGANIC CHEMISTRY 7, 493–496 (1978)

A Possible Biogenetic-Type Synthesis of 2-Methylisoflavones

AMOLAK C. JAIN,[1] RAJESH KHAZANCHI, AND RAMESH C. GUPTA

Department of Chemistry, Himachal Pradesh University, Simla 171005, India

Received September 6, 1978

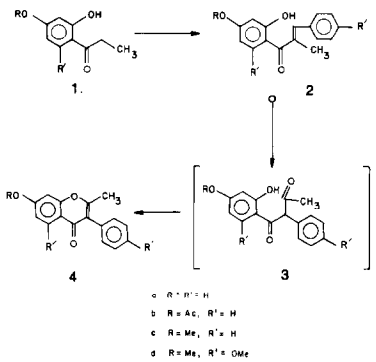
Two α-methylchalcones (**2c** and **2d**), on oxidation with thallium (III) nitrate, afford the corresponding 2-methylisoflavones (**4c** and **4d**, respectively), **4c** being the natural isoflavone isolated from *Glycyrrhiza glabra*. This synthesis is the first of 2-methylisoflavones starting from α-methylchalcones, which could also be the precursors in Nature.

From the air-dried roots of the Indian grown *Glycyrrhiza glabra*, Bhardwaj *et al.* (*1*) isolated three 2-methylisoflavones, namely, 2-methyl-7-hydroxy-isoflavone (**4a**), its acetate (**4b**), and its methyl ether (**4c**). This report is the first one of the occurrence of 2-methylisoflavone derivatives in Nature, although isoflavones with the 2-position free are known to occur in large number (*2*). The biogenesis of 2-methylisoflavones has been visualized by Bhardwaj *et al.* (*1*) as involving the linking of an acetate unit to a desoxybenzoin. This suggestion finds analogy in the laboratory synthesis involving the Perkin acylation reaction of desoxybenzoins (*3*). Since isoflavones with the free 2-position are known to be formed in Nature through rearrangement of one of the benzene rings in 2′-hydroxychalcones (*4*), we postulate that even 2-methylisoflavones could arise in Nature in a similar manner, involving the formation of α-methylchalcones (**2**). The role of α-hydroxychalcones and α-methoxychalcones has recently been emphasized by Roux *et al.* (*5*). It is therefore likely that α-methylchalcones (**2**) are also formed in Nature and that they subsequently undergo rearrangement of one of the aryl groups to give the intermediate diketones (**3**) which finally cyclize to 2-methylisoflavones.

To provide support for the above hypothesis, two α-methylchalcones (**2c** and **2d**), prepared from the corresponding propiophenone derivatives, (**1c** and **1d**, respectively) (*6*, *7*), have been converted into the corresponding 2-methylisoflavones (**4c** and **4d**) using thallium (III) nitrate in methanol. This reagent had been used earlier for the synthesis of isoflavones with the 2-position free (*8*, *9*). The isoflavones (**4c** and **4d**) were characterized by their uv and nmr spectra. In order to avoid any ambiguity in the structures of **4c** and **4d** in light of the work by McKillop *et al.* (*11*), **4c** has been prepared unambiguously by the method of Baker and Robinson (*3*, *10*). The two samples were compared directly by mmp, tlc, and ^{13}C nmr spectra. It was found that the two samples are identical. The ^{13}C nmr data on the two samples are given in Table 1; assignment of chemical shifts to basic isoflavone structure is based on a recent publication by Wenkert and Gottlieb (*12*).

[1] To whom correspondence should be addressed.

0045-2068/78/0074-0493$02.00/0



Synthesis of 2-Methylisoflavones

TABLE 1

CARBON SHIFTS OF ISOFLAVONES

Carbon	δ (ppm)[a]	
	4c prepared by TTN method	4c prepared by old method[b]
2	163.6	163.6
3	123.2	123.1
4	175.9	175.7
4a	117.2	117.1
5	127.5	127.4
6	113.9	113.8
7	162.4	162.4
8	99.8	99.7
8a′	157.3	157.3
1′	130.3	130.3
2′	127.5	127.3
3′	128.1	128.1
4′	133.1	133.0
5′	128.1	128.1
6′	127.5	127.3
OMe	55.7	55.6
Me	19.4	19.3

[a] The δ values are in ppm relative to TMS; δ(TMS) − δ($CDCl_3$) + 76.9 ppm.

[b] See Refs. (*3*, *10*).

EXPERIMENTAL

The melting points were recorded in a sulfuric acid bath at an altitude of ~2100 m and are uncorrected. Ultraviolet spectra were recorded in methanol. The nmr spectra were taken on a Varian A-60D instrument with TMS as internal standard and $CDCl_3$ as solvent. The R_f values are those recorded on tlc plates coated with silica gel G, using benzene:ethyl acetate (4:1) as the solvent system, alcoholic ferric chloride as

the spraying agent for chalcones, and 10% aqueous H_2SO_4 as the spraying agent for isoflavones. The light petroleum used had boiling range 60–80°C.

α-Methyl-2'-hydroxy-4,4',6'-trimethoxychalcone (**2d**)

To a solution of 2-hydroxy-4,6-dimethoxypropiophenone (*7*) (**1d**, 2.4 g) in ethanol (50 ml) was added an aqueous solution of potassium hydroxide (6 g in 6 ml of water) and anisaldehyde (1.3 ml). The resulting mixture was heated on a boiling water bath for 30 min, left at room temperature for 48 hr, diluted with water (150 ml), and extracted with light petroleum to remove the unreacted anisaldehyde. The aqueous solution was acidified and the solid filtered and washed first with 5% aqueous sodium carbonate and then with water to obtain **2d**. It crystallized from ethanol as yellow crystals (1.5 g); mp 100–101°C; R_f 0.45; violet ferric reaction; uv λ_{max} 238 and 294 nm; ^{1}H nmr δ2.16 (d, J = 1 Hz, 3H, $-CH_3$), 3.73, 3.83 (2s, 9H, 3-OCH_3), 6.0 (d, J = 2.5 Hz, 1H, H-5'), 6.19 (d, J = 2.5 Hz, 1H, H-3'), 6.83 (q, J = 1 Hz, 1H, H-β), 6.96 (d, J = 9 Hz, 2H, H-3,5), 7.43 (d, J = 9 Hz, 2H, H-2,6), 12.10 (s, 1H, chelated OH) ppm.

Anal. Calcd for $C_{19}H_{20}O_5$: C, 69.5; H, 6.1. Found: C, 69.2; H, 6.1.

2-Methyl-5,7,4'-trimethoxyisoflavone (**4d**)

To a well-stirred solution of the above chalcone (**2d**, 0.66 g) in methanol (120 ml) was slowly added thallium (III) nitrate (0.86 g). The stirring was continued at room temperature for 4 hr, after which 10% HCl (6 ml) was added. The resulting mixture was refluxed for 3 hr; inorganic solid was filtered off, and the filtrate was evaporated to dryness. The residue was extracted with benzene and the insoluble part subjected to column chromatography. Elution with benzene:ethyl acetate (9:1) gave **4d** which crystallized from methanol as white flakes (0.1 g); mp 175°C [lit. (*10*), mp 175–176°C]; R_f 0.35; uv λ_{max} 258 and 315 nm (log ε 4.17 and 4.0, respectively); ^{1}H nmr δ2.13 (s, 3H, $-CH_3$), 3.94 (s, 9H, 3-OCH_3), 6.34, 6.44 (dd, J_{ortho} = 8 Hz, J_{meta} = 2 Hz, 2H, H-6,8), 6.93 (d, J = 9 Hz, 2H, H-3',5'), 7.53 (d, J = 9 Hz, 2H, H-2',6') ppm.

α-Methyl-2'-hydroxy-4'-methoxychalcone (**2c**)

2-Hydroxy-4-methoxypropiophenone (*9*) (**1c**, 2.1 g) and benzaldehyde, (1.7 g) were condensed in aqueous ethanolic potassium hydroxide (6 g/6 ml/50 ml) as described above. However, heating was carried out for 1 hr and the mixture left at room temperature for 72 hr. The product was purified by column chromatography using silica gel as the adsorbant. Elution with light petroleum gave a yellow oil which, after standing in ice chest for 24 hr, solidified to afford **2c**. It crystallized from methanol as yellow crystals; mp 95°C; R_f 0.9; brown ferric reaction; uv λ_{max} 235 and 345 nm (log ε 3.22 and 4.39, respectively); ^{1}H nmr δ2.18 (broad s, 3H, $-CH_3$), 3.92 (s, 3H, $-OCH_3$), 6.43 (d, J = 1 Hz, 1H, H-3'), 6.56 (d, J = 8.5 Hz, 1H, H-5'), 6.67 (q, 1H, H-β), 6.87 (d, J = 7 Hz, 1H, H-6'), 7.46 (*m*, 5H, C_6H_5) ppm.

Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.1; H, 6.01. Found: C, 76.4; H, 6.0.

2-Methyl-7-methoxyisoflavone (**4c**)

The above chalcone (**2c**, 0.55 g) was oxidized with thallium (III) nitrate (0.86 g) in methanol (100 ml) as described earlier. The product was directly crystallized from

methanol whereby **3c** was obtained as colorless flakes (0.2 g); mp 144°C [lit. (*1*) mp 142–143°C]; R_f 0.62; uv λ_{max} 245 and 295 nm (log ε 4.34 and 4.11, respectively); ^{1}H nmr δ2.26 (s, 3H, $-CH_3$), 3.96 (s, 3H, OCH_3), 6.75, 6.94 (dd, J_{meta} = 2 Hz, J_{ortho} = 9 Hz, 2H, H-6,8), 7.27 (m, 5H, C_6H_5), and 8.01 (d, J = 9 Hz, 1H, H-5) ppm.

The above compound agrees in mmp, tlc, and ^{13}C nmr with the one prepared unambiguously by the method of Baker and Robinson (*3*, *10*).

ACKNOWLEDGMENTS

The authors express their sincere gratitude to the University Grants Commission, New Delhi, for the award of the National Fellowship to A.C.J. and of JRF to R.K. and to the Council of Scientific and Industrial Research, New Delhi, for JRF to R.C.G. They are also thankful to Dr R. J. Abraham of the University of Liverpool for recording the ^{13}C nmr spectra reported in this paper.

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