SYNTHETIC ANALOGS OF NATURAL FLAVOLIGNANS. XIV. SYNTHESIS AND TRANSFORMATIONS OF 2′-SUBSTITUTED CHALCONES AND CHALCONEPOXIDES

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2′-Substituted chalcones and chalconepoxides have been synthesized. Their reactions with BF_3 etherate and hydrazine hydrate were studied.

Key words: chalcones, chalconepoxides, isoflavones, synthesis.

Isoflavones are isomeric with flavones and originate biosynthetically from a single precursor, diphenylpropane. Isoflavones and their heterocyclic analogs are interesting as physiologically active compounds with various applications.

Numerous methods for synthesizing isoflavones are known. Starting compounds are usually 2-hydroxydeoxybenzoins or 2′-hydroxychalcones.

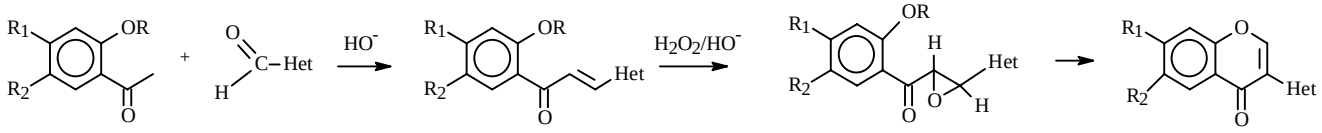
House et al. [1] studied in detail the BF_3·etherate-catalyzed isomerization of chalconepoxides into formyldeoxybenzoins. This method was used first by Bhrara et al. [2] and then by other groups [3-5] to synthesize isoflavones from 2′-substituted chalconepoxides. Isomerizations catalyzed by conc. HCl or BF_3·etherate are considered to be the best ones for synthesizing isoflavones because these reactions are facile and give good yields.

Various methods can be used to show that substituted 2′-benzyloxychalconepoxides are converted by conc. HCl or BF_3·etherate into not only isoflavones but also 3-hydroxyflavononones, depending on the nature of the substituents [2, 6, 7].

Therefore, it seemed interesting to study the reaction of 2′-substituted chalconepoxides with BF_3·etherate. The starting 2′-substituted chalcones are easily prepared via alkaline condensation of 2-substituted acetophenones with the corresponding hetarylaldehydes [8].

The chalconepoxides needed for this rearrangement are usually prepared by oxidation of 2′-substituted chalcones with hydrogen peroxide in alkaline medium.

The reaction of chalcones **2a** and **-e** and **3a**, **-c**, and **-d** with hydrogen peroxide in alkaline medium gives epoxides **4a** and **-e** and **5a**, **-c**, and **-d** in good yields.

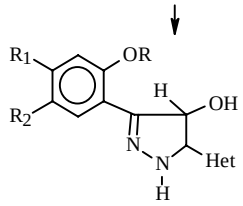


1e, 2a, e, 3a, c, d

4a, e, 5a, c, d

1e: R = CH_2OCH_3, R_1 = OCH_2OCH_3, R_2 = H, Het = A
2, 4, 7e: R = CH_2OCH_3, R_1 = OCH_2OCH_3, R_2 = H, Het = B
3, 5, 6, 8a: R = $OCH_2C_6H_5$, R_1 = R_2 =H, Het =C
c: R=$OCH_2C_6H_5$, R_1 = OCH_3, R_2 = H, Het = C
d: R = $OCH_2C_6H_5$, R_1 = H, R_2 = F, Het = C

Het: A = 6-chloro-1,3-denzodioxan-8-yl
B = 1,4-benzodioxan-6-yl
C = 1,5-benzodioxepan-7-yl



7a, e, 8a, c

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TABLE 1. Properties of **1**-**8**

Compound	Yield, %	mp, °C	Crystallization solvent
1c	40	110-112	EtOH
2a	90	111-112	EtOH
3a	90	117-118	EtOH
3c	73	90-91	EtOH
3d	86	122-123	EtOH
4a	82	120-121	EtOH
5a	87	101-102	EtOAc
5c	73	88-90	EtOH
5d	91	151-152	EtOAc
6a	49	185-186	EtOAc
6d	64	193-194	EtOAc
7a	50	170-171	C_6H_6
7e	27	136-137	C_6H_6/hexane
8a	67	149-150	C_6H_6
8c	63	206-207	C_6H_6

TABLE 2. Proton Chemical Shifts in PMR Spectra of 2′-Substituted Chalcones

Compound	PMR spectrum, δ, ppm, J/Hz										
	phenol protons						heterocycle protons				
	C_6H_5--CH_2O-2	R_1-3	R_2-4	R_3-5	H-6	COCH=CH dd (15-16)	H-5 or H-6	H-7 and H-8	H-8 or H-9	CH_2-2, s	CH_2-4, s or O(CH_2)nO
1e	3.50 5.25	6.83 d (1.5)	3.50 5.29	6.78 dd (8.0; 1.5)	7.69 d (8.0)	7.52; 7.82	6.96	7.43	-	5.21	4.87
2a	5.42 (5.6); 7.70	7.0-8.0 m	7.0-8.0 m	7.0-8.0 m	8.09 d (11.5)	7.66; 7.93 (6.6; 8.3)	7.20 m	7.20 m	7.20 m	-	4.48
3a	5.16 7.35	7.5-6.9 m	7.5-6.9 m	7.5-6.9 m	7.70	7.28; 7.56	7.5-6.9 m	7.5-6.9 m	6.86 d (8.0)	-	4.24 t 2.21 q
3c	5.13; 7.34	6.50 d	3.86	6.57 dd (9.0; 2.5)	7.85 (9.0)	7.23; 7.53	6.86	7.05	6.86 m	-	4.234 t 2.2 q
3d	5.12; 7.35	6.8-7.4 m	6.8-7.4 m	-	6.8-7.4 m	7.13; 7.56	6.8-7.4 m	6.8-7.4 m	6.8-7.4 m	-	4.24 t 2.22 q

Chalcones **1**, **2**, and **3** are yellow or orange crystalline compounds that are very soluble in organic solvents and have quite high melting points. Epoxides **4** and **5**, in contrast with the starting chalcones **1**, **2**, and **3**, are colorless crystalline compounds.

The PMR spectra of **1**, **2**, and **3** exhibit signals characteristic of olefinic protons, the chemical shifts of which lie at 7.0-8.0 ppm. The spin—spin coupling constants (SSCC, J = 15.8-16.1 Hz) indicate that the chalcones have the trans configuration (Table 2).

The PMR spectra of **4** and **5** have signals characteristic of methine protons in the oxirane ring as doublets with small SSCC (J = 1.76-1.83 Hz). One of the signals is located at 4.24-4.26 ppm; the other, at 4.30-4.35 ppm (Table 3).

Rearrangement of **5a** and **-d** by BF_3·etherate gives 1,5-benzodioxepane analogs of isoflavone **6a** and **-d** in good yields.

The PMR spectra of isoflavones **6a** and **-d** contain signals at weak field for protons H-2 and H-5 of the chromone ring. These protons are deshielded by the oxygen atoms of the pyrone ring.

TABLE 3. Proton Chemical Shifts in PMR Spectra of 2′-Substituted Chalconepoxides

Compound	PMR spectrum, δ, ppm, J/Hz							
	phenol protons						heterocycle protons	
	C_6H_5--CH_2O·2	R_1-3	R_2-4	R_3-5	H-6	epoxy group	H-5, H-6, H-7, H-8, H-9	CH_2-2, CH_2-4, s $O(CH_2)nO_n$
4a	5.27; 7.56	7.33	7.4-7.8	7.4-7.8	8.12	4.64; 4.11	7.05 (H-5, H-7, H-8)	4.43
5a	5.01; 7.23	6.95	7.46	7.02	7.78	4.40; 3.92 (1.95)	6.87(d, 1H, J = 2.0, H-6); 6.73(dd, 1H, J = 8.0; 2.0, H-8); 6.88(d, 1H, J = 8.0, H-9)	4.17 t, 2.17 q
5c	4.98; 7.23	6.49	3.81	6.53	7.89	4.43; 3.89 (1.95)	6.86(d, 1H, J = 1.95, H-6); 6.72(dd, 1H, J = 8.30; 1.95, H-8); 6.87(d, 1H, J = 8.3, H-9)	4.17 t, 2.17 q
5d	4.99; 7.24	7.20	7.20	-	8.30	4.48; 3.91 (1.95)	6.84(d, 1H, J = 2.0, H-6); 6.73(dd, 1H, J = 8.0; 2.0, H-8); 6.88(d, 1H, J = 8.0, H-9)	4.17 t, 2.17 q

TABLE 4. Proton Chemical Shifts in PMR Spectra of 4-Hydroxypyrazolines in $CDCl_3$

Compound	PMR spectrum, δ, ppm, J/Hz										
	phenol protons					pyrazoline protons				heterocycle protons	
	OR-2	H-3	R_2-4	R_3-5	H-6	N-H,	OH-4, d	H-4, dd	H-5, d	(H-7)-6 (H-9)-8 (H-10)-9	$O(CH_2)nO$
7a	5.12 s; 7.34 m	6.8-7.3 m	6.8-7.3 m	6.8-7.3 m	7.92 d (9.29)	5.94	3.16 (5.37)	5.05 (5.37; 3.42)	4.61 (5.37; 3.42)	6.8-7.3 m	4.23 s
7e	4.92 k (7); 3.20 s	6.7-6.9 m	5.20 s 3.47 s	6.7-6.9 m	7.82 d (9.28)	6.71	3.20 (3.4)	4.27 (3.4; 2.2)	3.97 (2.2)	6.7-6.9 m	4.27 s
8a	5.12 s; 7.35 m	6.8-7.3 m	6.8-7.3 m	6.8-7.3 m	7.97 dd (9.2; 3.0)	5.93	3.20 (3.4)	5.10 (5.3; 3.4)	4.62 (5.3)	6.8-7.3 m	4.18t 2.17 q
8c	5.09 s; 7.33 m	6.54 d (2.5)	3.80 s	6.59 dd (2.28; 2.5)	7.83 d (9.28)	5.83	3.12 (3.42)	5.0 (5.37; 3.42)	4.58 (5.37)	6.89	4.18 t (5.86); 2.16 q (5.86)

The reaction of 2′-substituted chalconepoxides **4** and **5** with hydrazine hydrate involves opening of the oxirane ring and formation of a pyrazoline ring. Thus, brief heating of **4a** and **-e** and **5a** and **-c** with hydrazine hydrate forms the 4-hydroxypyrazoline ring of **7a** and **-e** and **8a** and **-c**. The structures of **7a** and **-e** and **8a** and **-c** are consistent with their PMR spectra (Table 4).

Thus, transformation of chalconepoxides into isoflavones by a Lewis acid makes possible broader application of epoxides. Chalconepoxides are readily converted to various types of flavonoids and other heterocyclic compounds.

EXPERIMENTAL

The course of the reactions and the purity of the products were monitored by TLC on Silufol UV-254 plates using benzene—ethanol (9:1). PMR spectra of **1-8** were measured in $CDCl_3$ on a WP-100 SY Bruker spectrometer.

2′-Substituted Chalcones (1e, 2a and -e, 3a, -c, -d). A hot solution of 2-benzyloxyacetophenone or 2,4-dimethoxymethoxyacetophenone (20 mmol) in alcohol was treated with the corresponding hetarylaldehyde (20 mmol) and NaOH solution (50%, 4.7 mL). The reaction mixture was held at room temperature for 20-40 h. The precipitate was suspended in water. The solution was acidified with acetic acid until it was neutral. The solid was filtered off and crystallized from alcohol.

1-(2,4-Dimethoxymethoxyphenyl)-3-(hetaryl)-2,3-epoxypropan-1-ones (4a and -e), 1-(2-Benzyloxyphenyl)-3-(1,5-benzodioxepan-7-yl)-2,3-epoxypropan-1-ones (5a, -c, and -d). A solution of (**2a** or **-e** or **3a**, **-c**, or **-d**) (6 mmol) in an acetone—methanol (15:4) mixture (80-100 mL) was treated with H_2O_2 solution (30%, 30 mL) and NaOH solution (2 N, 30 mL). After the color disappeared (12 h), the reaction mixture was diluted with water. The precipitate was filtered off and crystallized from a suitable solvent.

3-(1,5-Benzodioxepan-7-yl)-chromone (6a). A solution of **5a** (10 mmol) in absolute benzene (150 mL) was treated with BF_3·etherate (2 mL) and boiled for 25-30 h. The completion of the reaction was determined by TLC. The solution was washed with water. The benzene was evaporated under vacuum from a water aspirator. The precipitate was crystallized from ethylacetate. PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): chromone ring: 7.99 (1H, s, H-2), 8.31 (1H, dd, J = 8.3, 0.98, H-5), 7.42 (1H, t, d, J = 8.3, 0.98, H-6), 7.68 (1H, t, d, J = 8.3, 0.98, H-7), 7.46 (1H, dd, J = 8.3, 0.98, H-8); benzodioxepane ring: 4.26 (4H, t, J = 5.87, CH_2-2 and CH_2-4), 2.21 (2H, q, J = 5.87, CH_2-3), 7.21 (1H, d, J = 2, H-6), 7.15 (1H, dd, J = 7.8, 2.0, H-8), 7.02 (1H, d, J = 7.8, H-9).

3-(1,5-Benzodioxepan-7-yl)-6-fluorochromone 6d was prepared analogously to **6a**. PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 7.99 (1H, s, H-2), 7.93 (1H, dd, J = 9.16, 2.93, H-5), 7.43 (2H, m, H-7,8); benzodioxepane ring 4.24 (4H, t, J = 5.8, CH_2-2 and CH_2-4), 2.21 (2H, q, J = 5.8, CH_2-3), 7.99 (1H, d, J = 2.0, H-6), 7.15 (1H, dd, J = 8.43, 2.0, H-8), 7.01 (1H, dd, J = 8.43, 0.7, H-9).

3-(2-Substituted phenyl)-4-hydroxy-5-hetaryl Pyrazolines 7a and -e and 8a and -c. A solution of the corresponding epoxide of chalcones **4a** and **-e** and **5a** and **-c** (4 mmol) in ethanol (50 mL) was treated with hydrazine hydrate (80%, 0.4 mL) and boiled for 0.5-5 h. The precipitate was filtered off and crystallized from benzene.

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