Albert Lévai

Department of Organic Chemistry, University of Debrecen, P.O. Box 20, H-4010 Debrecen, Hungary
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Dedicated to Professor Dr. José A. S. Cavaleiro on the occasion of his 60th birthday.

A comparative study of the epoxidation of homoisoflavones (3-benzyl-4-chromones) **1-4** has been performed by various oxidizing agents, *víz.* epoxidation with isolated dimethyldioxirane (Method A), with alkaline hydrogen peroxide (Method B), and with sodium hypochlorite (Method C) to obtain the epoxides **4-8**. Compounds **2** and **3** have also been oxidized with a combination of dimethyldioxirane and Jacobsen's Mn(III)salen catalysts (*R,R*)-**11** and (*S,S*)-**11** to afford 3-benzoyl-4-chromones **9** and **10**. Structures of all new compounds have been elucidated by microanalyses, ir and nmr spectroscopic measurements.

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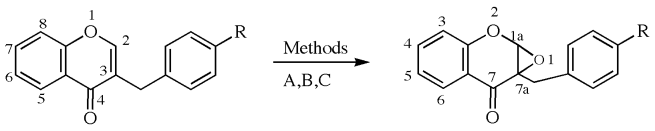
Homoisoflavones (3-benzyl-4-chromones or 3-benzyl-4*H*-benzopyran-4-ones) were isolated from various plants as naturally occurring chromone derivatives [1-3]. For the synthesis of these oxygen-heterocyclic compounds, various procedures have been worked out. Homoisoflavones were synthesized by the ring closure of 2'-hydroxydihydrochalcones first by Farkas *et al.* [4] and later in other laboratories [5-8]. A simple and convenient procedure is based on the exocyclic-endocyclic double bond migration of 3-arylmethylene-4-chromanones. Andrieux *et al.* conducted this double bond transposition by rhodium trichloride trihydrate [9]. Donnelly *et al*. converted 3-benzylidene-4-chromanones into 3-benzyl-4-chromones on treatment with potassium carbonate in dimethylformamide at 153° [10]. In our previous study, we have investigated the piperidine-catalyzed reaction of 4-chromanone and benzaldehydes [11]. It has been found that if a strongly electron-withdrawing substituent was present in the aromatic aldehyde, 3-benzyl-4-chromones were obtained as sole isolable products instead of the expected 3-benzylidene-4-chromanones. As a result of the development of these synthetic methods, homoisoflavones became easily available compounds for various chemical transformations.

Formerly we have demonstrated that the isolated dimethyldioxirane (DMD) [12] is a convenient oxidant for the epoxidation of variously substituted flavones [13], isoflavones [14] and isoflavone glycosides [15], providing their epoxides in excellent yields without any purification. It has also turned out that the substitution patterns of the aromatic rings are almost without influence either on the course of the epoxidation or on the yields of the isolated epoxides. As a continuation, it appeared expedient to perform similar epoxidation study of the homoisoflavones.

3-Benzyl-4-chromones **1-4** were allowed to react with isolated DMD (0.05-0.1 *M* acetone solution) according to the Method A. The progress of the reaction was monitored by thin layer chromatography (tlc), and new batches of DMD were added in 24 hour intervals until the complete conversion of the starting homoisoflavones were detected (14 days). Although a complete conversion of the starting material has taken place, the epoxides **5-8** could only be isolated in medium (32-40%) yields by column chromatography (Scheme 1). In the course of the reaction several minor products were detected in the solution by tlc, however, none of them could be isolated. We suppose that by-products or overoxidized products were formed along with the formation of the epoxides **5-8** as major products, as observed by us in the case of the dimethyldioxirane oxidation of the isomeric 3-arylidene-4-chromanones [16]. This may be the reason for the relatively low yields (*cf.* Experimental).

Scheme 1



1-4

1,5: R = H
2,6: R = Cl

5-8

3,7: R = Br
4,8: R = NO_2

Compounds **2** and **3** have also been attempted to epoxidize with 3-chloroperoxybenzoic acid as another electrophilic oxidant. However, from the intractable crude mixtures with substantial amount of the starting materials, no particular product could be isolated. For this reason, these experiments have not been included in the Eperimental of this paper.

To improve the yield of the epoxidation, utilization of nucleophilic oxidants has also been investigated. Recently we have used alkaline hydrogen peroxide and sodium hypochlorite for the epoxidation of 2-substituted isoflavones [17] which provided the corresponding epoxides in relatively good yields (66-88%).

Compounds **1-4** dissolved in methanol were oxidized with a mixture of 30% hydrogen peroxide and sodium hydroxide (Method B) to afford epoxides **5-8** (Scheme 1). The yields were quite similar to those obtained with DMD (Method A). Homoisoflavones **1-4** have also been

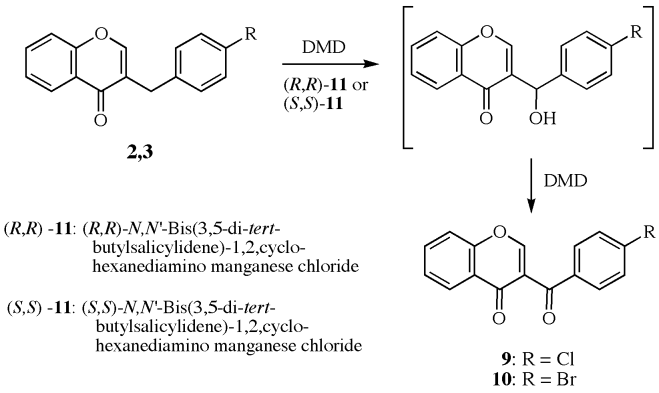
epoxidized with sodium hypochlorite (Method C) as another nucleophilic oxidant in pyridine solution (Scheme 1). However, the yield could not be improved by using this oxidant (*cf.* Experimental). A possible reason of this finding may be the decomposition of these chromone derivatives under alkaline reaction conditions.

The structures of epoxides **5-8** have been elucidated by elemental analyses, ir, ^{1}H and ^{13}C nmr spectroscopic measurements. In the ^{1}H nmr spectra, a singlet signal between 5.25 and 5.36 ppm is characteristic for the 1a-H proton as in the case of the related isoflavone epoxides [14,15,18,19]. Two doublets of the methylene protons of the benzyl group with *ca.* 15 Hz geminal coupling constant values are also found in each ^{1}H nmr spectrum. The ^{13}C chemical shifts for C-1a (*ca.* 80 ppm) and for C-7a (*ca.* 62 ppm) (*cf.* Experimental) corroborate the presence of the epoxide functionality.

The Jacobsen's Mn(III)salen complexes have been found to be efficient catalysts for the enantioselective epoxidation of isoflavones by using dimethyldioxirane as an oxygen donor [18,19]. It seemed expedient to investigate the utility of this combination for the enantioselective epoxidation of homoisoflavones.

Compounds **2** and **3** were allowed to react with DMD in the presence of (*R,R*)-**11** and (*S,S*)-**11** Mn(III)salen complexes at room temperature. However, instead of epoxides 3-benzoyl-4-chromones **9** and **10** were obtained as sole isolable products (Scheme 2). It should also be mentioned that a complete conversion of the starting homoisoflavones could not be reached even with a large excess of DMD (12 equivalents) during a long reaction time (12 days).

Scheme 2



An explanation of this result is that an oxygen insertion takes place on the benzylic carbon atom providing 3-(α-hydroxybenzyl)-4-chromones which are then further oxidized with DMD to offord 3-benzoyl-4-chromones (Scheme 2). One reason for this may be the bulkiness of the oxidized Mn(III)salen complex as the oxidant in this system. Its space demand makes impossible its attack at the double bond required for the epoxidation.

Formation of compounds **9** and **10** was observed on the dimethyldioxirane oxidation of 3-(4-chlorobenzylidene)-4-chromanone and 3-(4-bromobenzylidene)-4-chromanone [16]. 3-Benzoyl-4-chromones **9** and **10** prepared previously and in our present study proved to be identical in every respect.

In summary, we managed to use both electrophilic and nucleophilic oxidants for the epoxidation of homoisoflavones. Although the yields are moderate, previously unknown homoisoflavone epoxides became easily available by the utilization of these protocols. However, we failed to perform an enantioselective epoxidation of homoisoflavones by using Jacobsen's Mn(III)salen catalysts with dimethyldioxirane as oxygen source.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. ^{1}H and ^{13}C nmr spectra were recorded on a Gemini 200 (at 200 and 50 MHz for ^{1}H and ^{13}C, respectively) at ambient temperature (*ca.* 20°) in chloroform-d with tetramethylsilane as the internal standard. Ir spectra were obtained in KBr pellets with a Perkin-Elmer 16 PC instrument. Elemental analyses were measured in house on a Carlo Erba 1106 EA instrument. The tlc was performed on Kieselgel 60 F_{254} (Merck) layer with hexane:acetone (7:3 v/v) or 1,2-dichloroethane as eluents. The starting materials **1-4** were synthesized according to known procedures [6,8,11]. Dimethyldioxirane (DMD, as 0.05-0.1 *M* acetone solution) was prepared as described [12] and its peroxide content was determined iodometrically. Curox (potassium monopersulfate), the triple salt $2KHSO_5.KHSO_4.K_2SO_4$, was used as received, a generous gift from the Peroxid-Chemie GmbH (München, Germany).

General Procedure for the Epoxidation of Homoisoflavones **1-4**.

Method A.

Dimethyldioxirane (*approx.* 0.05-0.1 *M* acetone solution) was added to the appropriate homoisoflavone **1-4** (0.30 g, 0.95-1.22 mmoles) dissolved in anhydrous methylene chlroride (5.0 ml) at room temperature. The progress of the reaction was monitored by tlc and new batches of dimethyldioxirane were added in 24 hour intervals until the conversion of the starting material halted (14 days). The solvent was evaporated *in vacuo* and epoxides **5-8** were isolated by silica gel column chromatography using hexane:acetone (7:3 v/v) or 1,2-dichloroethane as eluents.

Method B.

Hydrogen peroxide (30%, 8.82 mmoles) was added to a cooled and stirred mixture of homoisoflavone **1-4** (0.30 g, 0.95-1.22 mmoles) and 4 *M* sodium hydroxide solution (1.0 ml, 4 mmoles) in methanol (30 ml). Stirring was continued at ambient temperature (*ca.* 20°) for 18 hours, then the solution was diluted with water, the precipitate was separated by filtration, washed with water, and recrystallized from methanol to obtain epoxides **5-8**.

Metrhod C.

Sodium hypochlorite (4.0-6.0 ml, 2.5-3.0 mmoles) was added to a stirred and cooled solution of homoisoflavone **1-4** (0.30 g,

0.95-1.22 mmoles) in pyridine (10.0 ml) and the agitation was continued at room temperature for 3 hours. The solution was diluted with water, the precipitated material was collected by filtration, washed with water, and purified by silica gel column chromatography using 1,2-dichloroethane as eluent to afford epoxides **5-8**.

1a,7a-Dihydro-7a-benzyl-7*H*-oxireno[*b*][1]benzopyran-7-one (**5**).

This compound was isolated as white needles in 38% (Method A), 31% (Method B), and 41% (Method C) yields, mp 89-90°; ir: ν 1684 (C=O) cm^{-1}; ^1H nmr: δ 3.21 (1H, d, J = 15.1 Hz, CH_2), 3.60 (1H, d, J = 15.1 Hz, CH_2), 5.25 (1H, s, 1a-H), 7.01-7-98 (m, 9 arom. H); ^{13}C nmr: δ 32.7, 62.5, 80.6, 117.9, 119.8, 123.3, 127.5, 127.6, 128.7, 130.3, 134.2, 136.2, 155.6, 189.2.

Anal. Calcd. for $C_{16}H_{12}O_3$: C, 76.21; H, 4.80. Found: C, 76.18; H, 4.82.

1a,7a-Dihydro-7a-(4-chlorobenzyl)-7*H*-oxireno[*b*][1]benzopyran-7-one (**6**).

This epoxide was obtained as white plates in 32% (Method A), 38% (Method B), and 45% (Method C) yields, mp 118-119°; ir: ν 1683 (C=O) cm^{-1}; ^1H nmr: δ 3.22 (1H, d, J = 15.1 Hz, CH_2), 3.52 (1H, d, J = 15.1 Hz, CH_2), 5.26 (1H, s, 1a-H), 7.04-7.96 (m, 8 arom. H); ^{13}C nmr: δ 32.1, 62.2, 80.6, 117.9, 119.7, 123.4, 127.5, 128.8, 131.5, 132.6, 133.2, 136.2, 155.5, 189.0.

Anal. Calcd. for $C_{16}H_{11}ClO_3$: C, 67.02; H, 3.87. Found: C, 67.06; H, 3.85.

1a,7a-Dihydro-7a-(4-bromobenzyl)-7*H*-oxireno[*b*][1]benzopyran-7-one (**7**).

This substance was prepared as pale yellow needles in 40% (Method A), 35% (Method B), and 42% (Method C) yields, mp 117-118°; ir: ν 1683 (C=O) cm^{-1}; ^1H nmr: δ 3.20 (1H, d, J = 15.0 Hz, CH_2), 3.50 (1H, d, J = 15.0 Hz, CH_2), 5.27 (1H, s, 1a-H), 7.02-7.98 (m, 8 arom. H); ^{13}C nmr: δ 32.2, 62.2, 80.5, 117.9,119.7, 121.3, 123.4, 127.5, 131.3, 131.8, 133.2, 136.2, 155.5, 189.9.

Anal. Calcd. for $C_{16}H_{11}BrO_3$: C, 58.03; H, 3.35. Found: C, 58.06; H, 3.34.

1a,7a-Dihydro-7a-(4-nitrobenzyl)-7*H*-oxireno[*b*][1]benzopyran-7-one (**8**).

This compound was obtained as pale yellow plates in 35% (Method A), 38% (Method B), and 39% (Method C) yields, mp 151-152°; ir: ν 1683 (C=O) cm^{-1}; ^1H nmr: δ 3.40 (1H, d, J = 15.0 Hz, CH_2), 3.54 (1H, d, J = 15.0 Hz, CH_2), 5.36 (1H, s, 1a-H), 7.02-8.20 (m, 8 arom. H); ^{13}C nmr: δ 32.9, 62.1, 80.6, 118.0, 119.6, 123.6, 123.8, 127.6, 131.1, 136.5, 142.1, 147.4, 155.4, 188.7.

Anal. Calcd. for $C_{16}H_{11}NO_5$: C, 64.65; H, 3.73. Found: C, 64.62; H, 3.75.

Oxidation of Homoisoflavones **2** and **3** by Dimethyldioxirane in the Presence of Jacobsen's Mn(III)salen Catalysts (*R*,*R*)-**11** and (*S*,*S*)-**11**.

Dimethyldioxirane (*ca*. 0.05-0.1 *M* acetone solution) was added to a stirred solution of the particular homoisoflavone **2** and **3** (0.30 g, *ca.* 1.20 mmoles) and Mn(III)salen complex (*R*,*R*)-**11** or (*S*,*S*)-**11** (20 mol%) dissolved in anhydrous methylene chloride (10.0 ml) and the stirring was continued at ambient temperature. The progress of the reaction was monitored by tlc and new batches of DMD was added in 24 hour intervals until no further conversion of the starting material was detected by tlc (12 days and 12 equivalents of DMD). The solvent was evaporated *in vacuo* and the 3-benzoyl-4-chromones **9** and **10** were isolated by silica gel column chromatography using hexane:acetone (7:3 v/v) as eluent.

3-(4-Chlorobenzoyl)-4*H*-1-benzopyran-4-one (**9**).

This substance was isolated in 15% [(*R*,*R*)-**11**] and in 19% [(*S*,*S*)-**11**] yields, mp 164-165°; Lit. [16] mp 163-165°.

3-(4-Bromobenzoyl)-4*H*-1-benzopyran-4-one (**10**).

This compound was separated in 17% [(*R*,*R*)-**11**] and 18% [(*S*,*S*)-**11**] yields, mp 160-161°; Lit. [16] mp 158-160°.

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