Stability and Chemical Reactivity of 7-Isopropoxyisoflavone (Ipriflavone)

Márton Varga,*[a] Sándor Bátori,[a] Mária Kövári-Rádkai,[a] Ildikó Prohászka-Német,[a] Magdolna Vitányi-Morvai,[a] Zsolt Böcskey,[a] Sándor Bokotey,[a] Kálmán Simon,[a] and István Hermecz[a]

Keywords: Drug research / Hydrolysis / Natural products / Oxidations / Photolysis

The stability (hydrolysis and oxidation) of ipriflavone (7-isopropoxyisoflavone, **1**) was studied under basic and acidic conditions in different solvents; the effects of irradiation were investigated in methanol. Identification of the isolated products enabled suggestions to be made concerning the mechanisms of decomposition.

Among the biologically active isoflavones, ipriflavone[1,2] (**1**) is used in human therapy[3,4] in several European countries and as an antiosteoporotic agent in Japan. The ongoing interest in this drug, with its unique mechanism of activity[5] (see Lien et al.[6] concerning phytoestrogenic isoflavonoids), demands a detailed understanding of its chemical stability and reactivity. In this context, we have investigated its hydrolysis, oxidation and photolysis. Because of the probable formation of a pyrylium ion (e.g., **15** or **41**) in acidic medium,[7–9] the expected products of these reactions can be different under basic and acidic conditions.

The alkaline hydrolysis and oxidation of the chromone ring have been widely used for structure elucidation of the isoflavone derivatives. The isoflavone ring of several natural pigments and other 4-chromone derivatives is opened on reaction with sodium or potassium hydroxide. This is followed by elimination of formic acid, to give the corresponding 1-(2-hydroxyphenyl)-2-phenylethanone derivatives.[10–24] The latter can be further hydrolysed with sodium or potassium hydroxide to furnish substituted phenylacetic acids, benzoic acids, and phenols.[25,26]

The oxidation of natural pigments with hydrogen peroxide or $KMnO_4$ gives substituted salicylic and benzoic acids and carbon dioxide.[27–30] The intermediates of the oxidation are probably the corresponding 2,3-epoxychromanone derivatives, which can be isolated under certain conditions.[31–35]

Results and Discussion

Hydrolysis

Alkaline hydrolysis of **1** in boiling 1 M NaOH solution yielded 1-(2-hydroxy-4-isopropoxyphenyl)-2-phenylethanone (**7**). This compound was also synthesised from the known 1-(2,4-dihydroxyphenyl)-2-phenylethanone[36,37] (**10**), with isopropyl bromide as alkylating agent. On treatment with 2 M NaOH at ambient temperature, the ketone **7** can be hydrolysed further (as shown in Scheme 1), and 2-hydroxy-4-isopropoxybenzoic acid (**12**) and benzoic acid (**13**) can finally be isolated. The formation of phenylacetic acid (**11**) would be expected from the suggested reaction pathway,[38] but its presence in the reaction mixture could not be proved by a number of different methods.

Ipriflavone (**1**) is stable in neutral and in mildly acidic solution. In concentrated H_2SO_4 at room temperature, however, the 2-propoxy group is hydrolysed and 7-hydroxyisoflavone (**16**) is obtained, together with other alkylated and/or sulfonated derivatives (**18**, **21**, **23**, **29**–**32**, and **24**–**28**) as minor products (see Scheme 2 and Table 1).

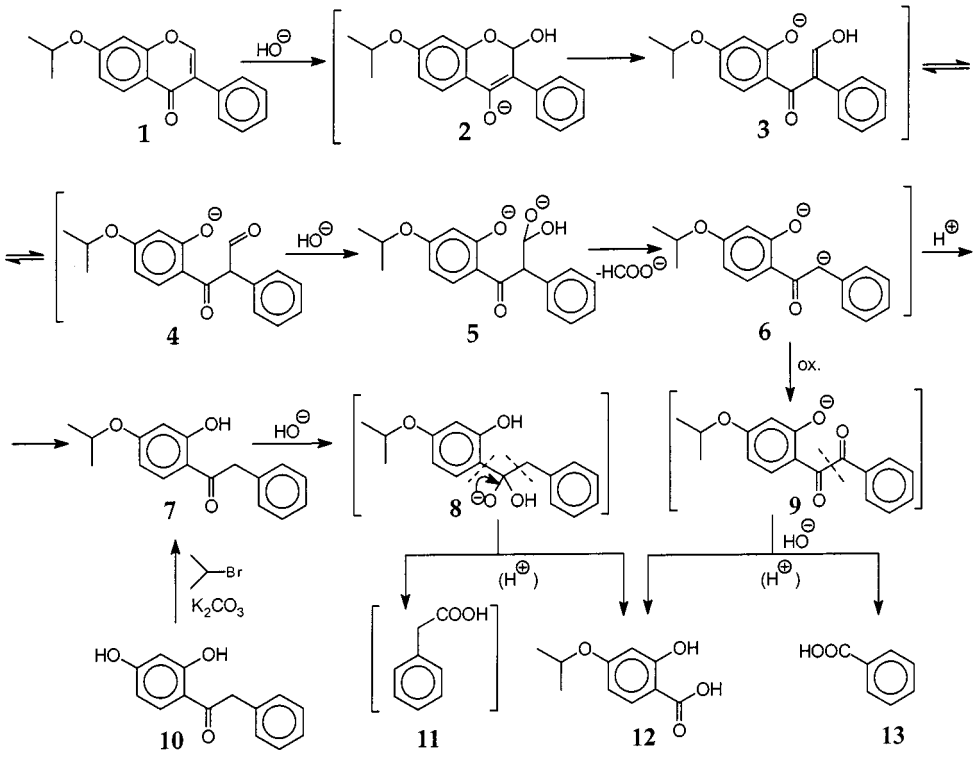
As suggested in the literature,[7–9] it is supposed that a benzopyrylium salt (such as **41**, see Scheme 4), formed in acidic medium, can be protonated further in the concentrated acid to give the dication **14**. The latter can easily lose the energetically relatively stable isopropyl cation (with simultaneous formation of **15**).

Elimination of the isopropyl cation was also indicated by quantum chemical calculations in which the semiempirical MNDO AM1 method[39] was used (see Figure 1). The behaviour of the C–O distance in the 2-propoxy group was studied. As the system is approached by a proton, the "normal" C–O bond length (1.46 Å) shortens (to 1.44 Å at an H–O distance of 2.0 Å), probably because of the formation of a nonclassical cation[40] between one of the methyl groups and the approaching proton (see the energy minimum at 2 Å). Further approach of the proton to the oxygen atom results in lengthening of the C–O bond (1.58 Å at an H–O distance of 1.2 Å), followed by a sudden breaking of the bond at an H–O distance of 1.1 Å.

According to the reaction pathway suggested in Scheme 2, the key intermediate of the alkylation (and sulfonation) process is the 7-hydroxyisoflavone **16**. Theoretically, if this compound were treated with 1 equiv. of isopropyl cation generated from other sources, it should give the same products, and in similar ratio, as given by the ipriflavone in concentrated H_2SO_4. We examined the treatment of **16** with 1 equiv. of 2-propanol under the same conditions

[a] CHINOIN Pharmaceutical and Chemical Works Co. Ltd., P. O. Box 110., 1325 Budapest, Hungary
Fax: (internat.) + 36-1/370-5412
E-mail: marton.varga@sanofi-synthelabo.com

  1434–193X/01/1020–3911 $ 17.50+.50/0



Scheme 1

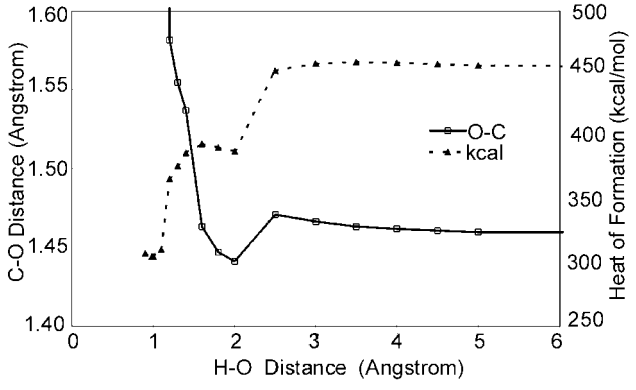


Figure 1. Energy profile and atomic distances during protonation of **1**

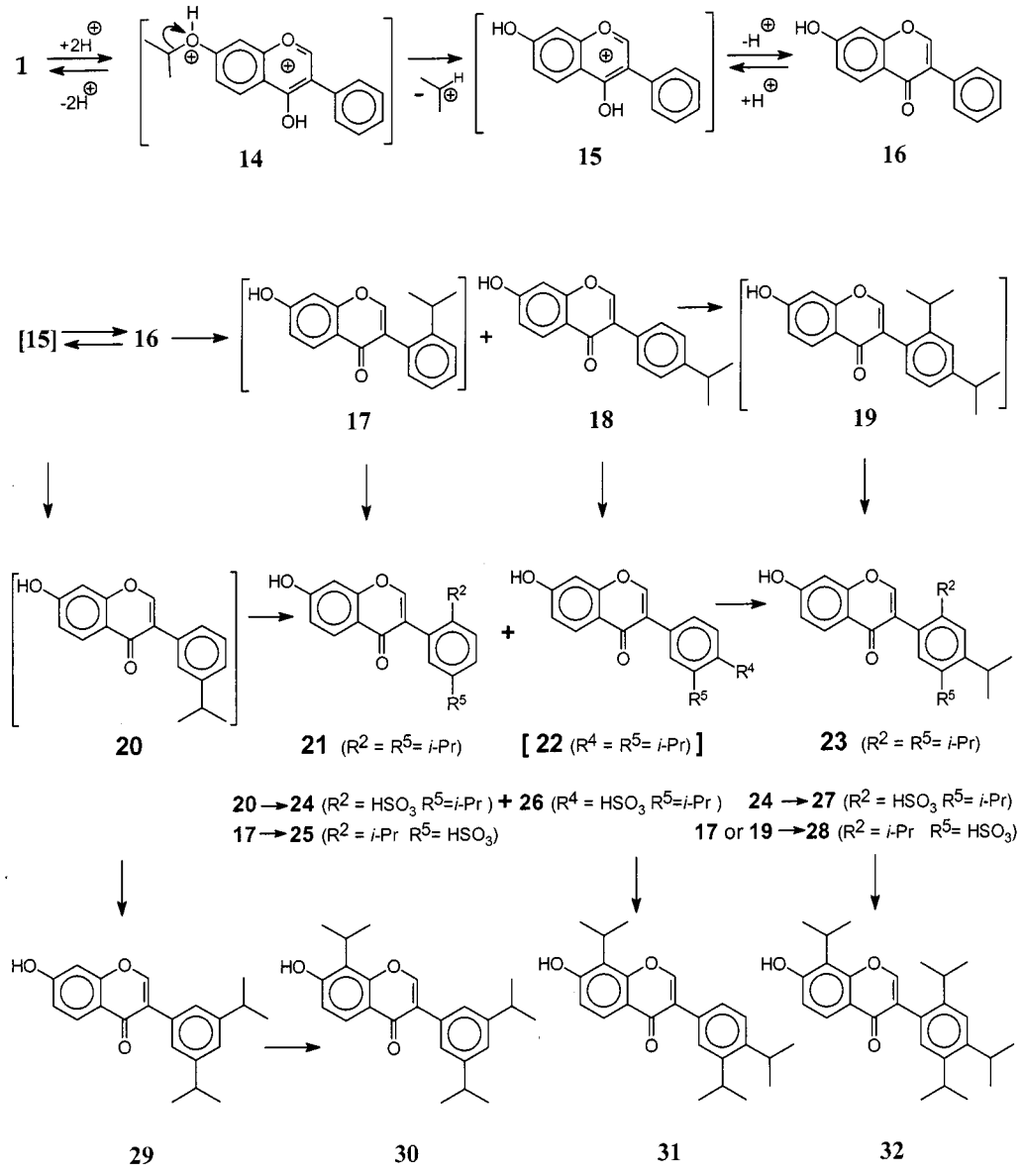
as in the case of ipriflavone, and we found the same product ratio and yields as formerly (see Table 1, sample 2). The monoalkylated derivatives **17** and **20** or the dialkylated compounds **19** and **22** were not isolated, very probably because their electrophilic substitution (alkylation and/or sulfonation) takes place more rapidly than their formation. The relatively high proportion of the derivatives **18**, **21**, and **29** among the reaction products demonstrated the steric difficulties involved in further substitution of these compounds. In accordance with our expectations, an increased amount of 2-propanol (2 equiv.) under the same reaction conditions resulted in the formation of more highly substituted products (e.g., **28**, **29**, and **30**) in higher ratios (see Table 1, sample 3). It is interesting that another type of electrophilic reaction, the sulfonation of 7-hydroxyisoflavone derivatives with chlorosulfonic acid, resulted in reaction at positions C-6 and/or C-8, but not in attack on the 3-phenyl ring.[41]

Table 1. HPLC analysis of the crude products from **1** or **16** in H_2SO_4; sample 1: crude product obtained from ipriflavone (**1**); sample 2: crude product obtained according to Method A (**16**/2-propanol, 1:1); sample 3: crude product obtained according to Method B (**16**/2-propanol, 1:2)

Compound no.	Retention time [min]	Sample 1 (%)	Sample 2 (%)	Sample 3 (%)
25 + **26**	6.9	ca. 0.0	0.31	0.1
24	7.9	0.34	ca. 0.0	ca. 0.0
28	15.4	2.26	2.99	11.7
27	16.4	4.28	5.1	7.64
16	18.8	38.83	35.08	5.45
18	25.5	27.21	28.05	8.72
21	28.9	8.87	9.66	11.95
29	31.4	14.62	13.9	33.7
23	33.9	0.12	0.18	4.6
31	34	1.22	1.24	ca. 0.0
30	36.6	ca. 0.0	0.47	7.75
32	38.1	0.5	0.48	0.83
others		1.75	2.56	7.54

Oxidation

When ipriflavone (**1**) was heated with 30% H_2O_2 in water at reflux temperature for 2 d there was no reaction.



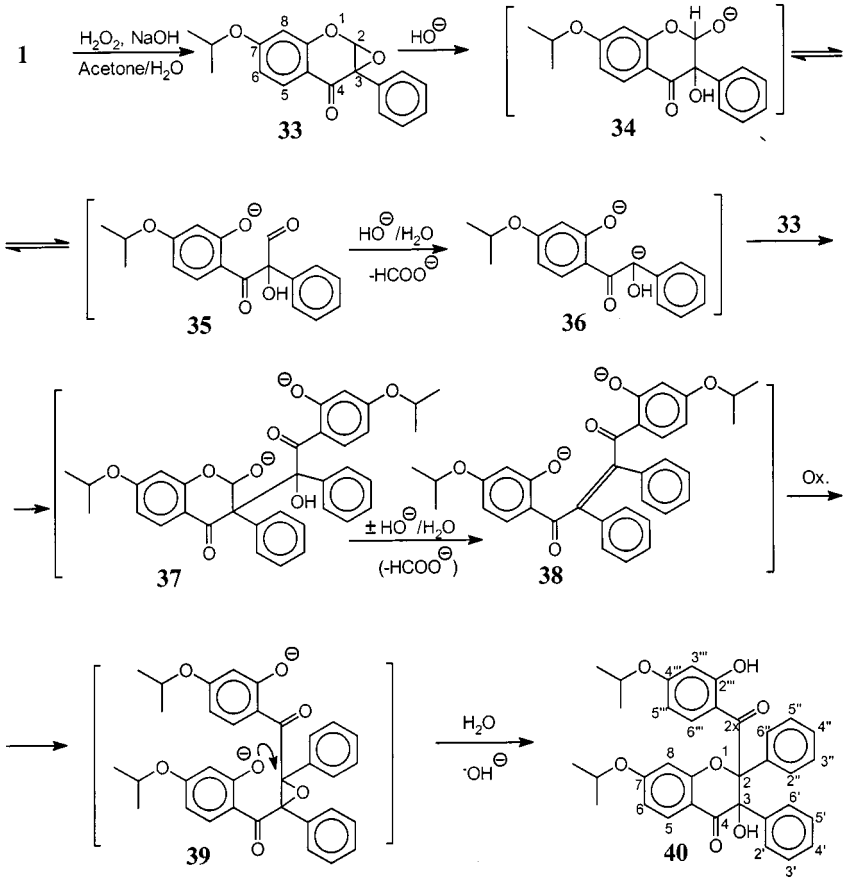
Scheme 2

Under similar reaction conditions in acetonitrile, however, 2,3-epoxy-7-isopropoxyisoflavanone (**33**) could be isolated in 5% yield (90% of the starting material **1** was recovered).

In acetone under alkaline conditions (1 M NaOH), however, oxidation of **1** with 30% H_2O_2 gave 2,3-epoxy-7-isopropoxyisoflavanone (**33**) in almost quantitative yield (95%, Scheme 3). Its structure was elucidated by IR and NMR measurements and by X-ray crystallography[42] (see Figure 2). Acetone is known to accelerate the oxidation of a double bond by formation of dimethyldioxirane,[43−46] which is very probably the real oxidising agent (though the involvement of other acetone peroxides[47−49] during the epoxidation process cannot be ruled out).

In a separate experiment, treatment of 2,3-epoxy-7-isopropoxyisoflavanone (**33**) with aq. NaOH for 2 weeks at room temperature gave a complex reaction mixture from which dimer **40** was isolated in low yield (16%). Its structure elucidation was performed by IR, ^1H, and ^{13}C NMR spectroscopy, mass spectrometry and also by X-ray crystallographic investigation.[42]

Although the isolated compound **40** is a substituted isoflavone (or flavone) derivative, it is formally a dimer of **35**. Similar structures, the first natural biisoflavonoids, were characterized by both spectroscopic and synthetic methods in 1988.[50−52] A suggestion for its formation is given in Scheme 3 (see above). According to this, the 2,3-epoxy derivative **33** decomposes, followed by reaction of the interme-



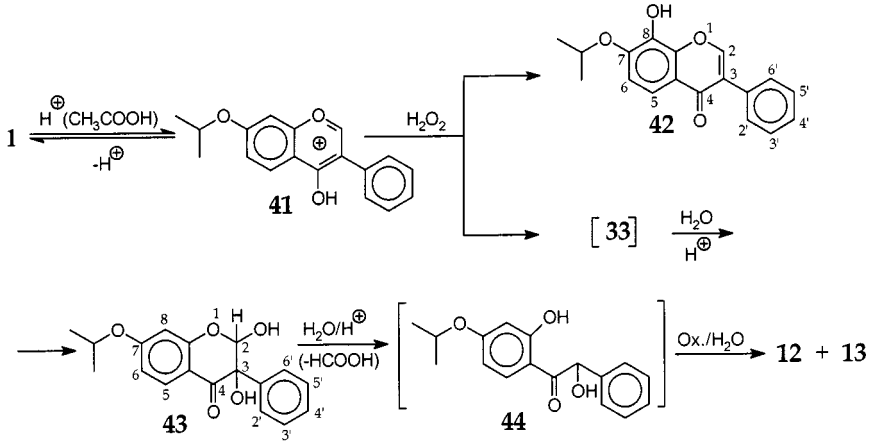
Scheme 3

diate **36** (formed during the decomposition) with **33** to give the very crowded 2-hydroxyisoflavanone derivative **37**. After decomposition of this derivative, the olefin intermediate **38** is formed, and after oxidation and ring closure, this gives the isolated derivative **40**. A similar ring closure and oxidation were recently described by Karton et al.[53] for the preparation of 3-hydroxyflavanone derivatives.

When the oxidation was performed in mildly acidic medium (acetic acid) with H_2O_2, no epoxide **33** was isolated, but the hydroxy derivatives **42** and **43** were obtained instead (Scheme 4).

The formation of 7-isopropoxy-8-hydroxyisoflavone (**42**) was in accordance with earlier results of other authors. 8-Hydroxyisoflavone derivatives have been prepared from isoflavone derivatives by oxidation with potassium peroxodisulfate.[54]

Formation of the 2,3-dihydroxychromanone derivative **43** very probably proceeded by means of acidic hydrolysis of



Scheme 4

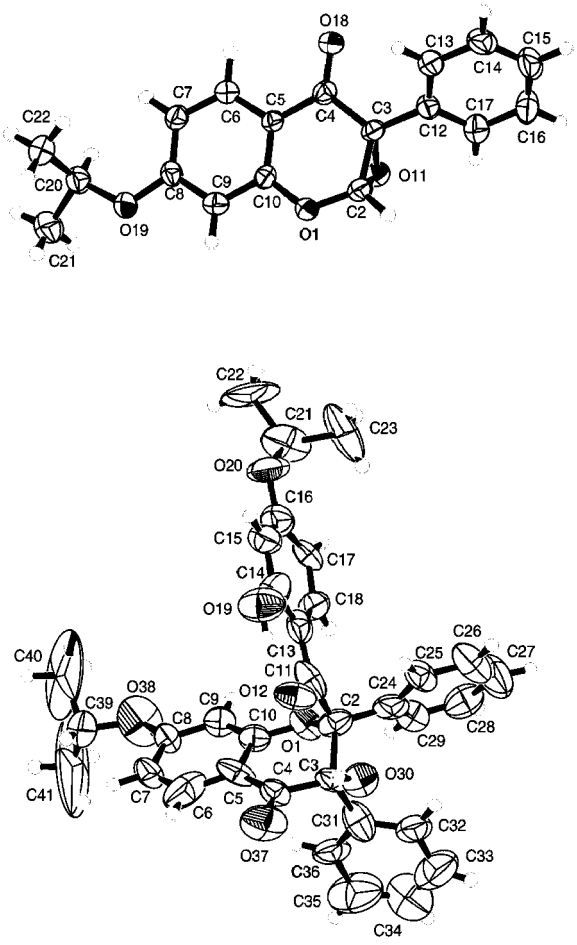


Figure 2. ORTEP diagrams of compounds **33** and **40**

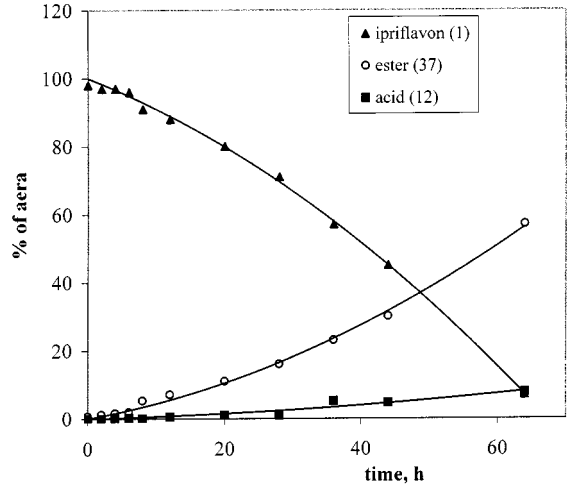
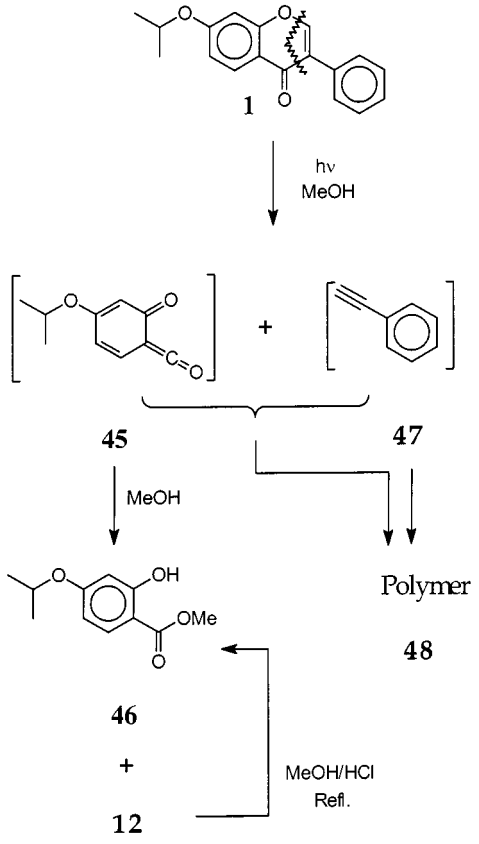


Figure 3. Irradiation of **1** in methanol

the epoxide **33**, the primary oxidation product. Although the 2,3-dihydroxy derivative **43** is sufficiently stable to be isolated, it can react further under the acidic oxidative conditions to give the decomposition products **12** and **13** obtained on alkaline hydrolysis of the parent compound **1** (see also Scheme 1). The 2,3-dihydroxy derivative **43** was obtained as a 44:56 mixture of two diastereomers. No separation or resolution was performed.



Scheme 5

Photolysis

Irradiation of ipriflavone (**1**) with a medium-pressure mercury lamp in methanol proceeded smoothly (see Figure 3) and resulted after 60 h in the formation of the same 2-hydroxy-4-isopropoxybenzoic acid (**12**) as had been obtained on basic hydrolysis or acidic oxidation. The other product isolated was the methyl ester **46**, which was synthesised separately from the acid **12** by esterification in methanol.

As far as we are aware, this is the first example of photolysis of the isoflavone skeleton. In addition to the isolated products **12** and **46** significant amounts of resin **48** were also produced. Structural study (TLC, IR, ^{1}H NMR, LC-MS, and elemental analysis) of this showed that this tarry material consisted of numerous unidentified compounds. The formation of the products **12**, **46**, and **48** can be explained by a mechanism such as that suggested in Scheme 5.

Conclusion

The chemical reactivity of ipriflavone was investigated. Hydrolysis in basic media gave 1-(2-hydroxy-4-isopropoxy-

phenyl)-2-phenylethanone (**7**) and its expected degradation products, 2-hydroxy-4-isopropoxybenzoic acid (**12**) and benzoic acid (**13**). In sulfuric acid, possibly because of formation of benzopyrylium ions **15** and **41**, we obtained the alkylated and/or sulfonated derivatives **18**, **21**, **23**, **29**−**32**, and **24**−**28** in addition to the key intermediate 7-hydroxyisoflavone (**16**). The suggested hydrolysis pathway was confirmed by quantum chemical calculations and by the products of separate treatment of **16** with 2-propanol in the presence of sulfuric acid.

The oxidation of **1** under basic conditions gave 2,3-epoxy-7-isopropoxyisoflavanone (**33**) and, surprisingly, a dimeric derivative **40**. The acidic oxidation products of **1** were 7-isopropoxy-8-hydroxyisoflavone (**42**) and the diastereomers of 2,3-dihydroxychromanone derivative **43**.

The first investigation of the photolysis of an isoflavone has been performed using ipriflavone. A reaction pathway accounting for the formation of the isolated 2-hydroxy-4-isopropoxybenzoic acid (**12**), its methyl ester **46** and the polymeric product **48** has been suggested. This study contributes to understanding of the stability and reactivity of the antiosteoporotic agent ipriflavone, and of other isoflavones in general.

Experimental Section

General Remarks: Thin layer chromatography was performed on Merck 60 F_{254} Kieselgel (0.2 mm) sheets. Kieselgel 60 (Reanal) was applied for column chromatography. Analytical HPLC was carried out with a Waters Millennium 32 single HPLC apparatus, with a Purospher RP-18 column (5 μm, 250 × 4.0 mm) using a gradient comprising A [= acetonitrile/0.01 M ammonium acetate (275:725)] and B (= acetonitrile). A linear gradient was run between two isocratic periods from 5 min (0% of B) to 20 min (60% of B) during a 40 min long elution. The ratio of components in the sample was calculated on the basis of absorption detected at 244 nm. − Melting points were determined with a Büchi 535 apparatus and are uncorrected. − A Unicam SP 8-200 was used to record the UV spectra (0.2 cm, ethanol; λ values in nm, log ε values in $Lmol^{-1}cm^{-1}$), a Bruker IFS-28 to record the IR spectra (KBr pellets, if not otherwise stated; $\tilde{\nu}$ values in cm^{-1}), and Bruker AC 200 and BRUKER DRX 400 spectrometers to record the ^1H and ^{13}C NMR spectra ($CDCl_3$ or [D_6]DMSO solutions; TMS standard; room temperature; *J* values are quoted in Hz). Mass spectra were obtained with a VG-TS mass spectrometer (70 eV, EI, direct inlet, if not indicated differently). − Microanalyses were performed with a Carlo Erba MOD 1106 apparatus and the crystallographic measurements were carried out using a FAST area detector diffractometer.

1-(2-Hydroxy-4-isopropoxyphenyl)-2-phenylethanone (7)

A. Treatment of Ipriflavone (1) with Sodium Hydroxide

Method A: Compound **1** (10.0 g, 35.7 mmol) was suspended in 1 M NaOH (200 mL), and the suspension was refluxed for 3 h. The cooled, dark brown suspension was then filtered, and the crystals were washed with water (10 mL) and dried. The crude product was dissolved in CH_2Cl_2 (4 mL) and purified by flash column chromatography (CH_2Cl_2/ethyl acetate) to give **7** (9.21 g, 95%), m.p. 81−82 °C (ref.[55] 82−84 °C). − $C_{17}H_{18}O_3$ (270.3): calcd. C 75.5, H 6.7; found C 75.2, H 6.7. − IR (KBr): $\tilde{\nu}_{max}$ = 3080, 3050, 3020, 2980, 2940, 1640, 1570, 1550, 1500, 1240, 1200, 1060, 780, 710, 690. − NMR: δ_H(400 MHz; [D_6]DMSO) = 1.27 [d, 6 H, *J* = 6.0, $(CH_3)_2CHO$], 4.33 (s, 2 H, CH_2), 4.70−4.76 [m, 1 H, $(CH_3)_2CHO$], 6.45 (d, *J* = 2.2 Hz, 1 H, 3-H), 6.51 (dd, *J* = 8.8, *J* = 2.2 Hz, 1 H, 5-H), 7.20−7.35 (m, 5 H, Ph), 8.00 (d, *J* = 8.8 Hz, 1 H, 6-H), 12.52 (s, 1 H, OH); δ_C(100 MHz; [D_6]DMSO) = 21.9 [$(CH_3)_2CHO$], 44.6 (CH_2), 70.3 [$(CH_3)_2CHO$], 102.3 (C-3), 108.5 (C-5), 113.1 (C-1), 126.9 (C-4′), 128.7 (C-3′, C-5′), 129.8 (C-2′, C-6′), 133.5 (C-6), 135.4 (C-1′), 164.4 (C-4), 164.8 (C-2), 202 (C=0).

Method B: Compound **1** (2.45 g, 8.75 mmol) was added to a mixture of 2 M NaOH solution (100 mL) and methanol (100 mL) and the mixture was then stirred for 4 h at room temperature. The mixture was neutralised with 5 M HCl and extracted with CH_2Cl_2. The organic layer was dried and the solvents evaporated in vacuum. After crystallisation from methanol we obtained **7** (1.30 g, 87%), The product was identical to that obtained by the previous method.

B. Alkylation of 1-(2,4-dihydroxyphenyl)-2-phenylethanone (10): Compound **10** (45.65 g, 0.2 mol) was dissolved in DMF (200 mL), and anhydrous K_2CO_3 (37.32 g, 0.27 mol) was added to the solution at room temperature, followed by isopropyl bromide (29.52 g, 22.5 mL, 0.24 mol). The reaction mixture was stirred at 65−70 °C for 5 h, cooled and poured into iced water (1 L). The beige crystals that precipitated were washed with water (3 × 100 mL) and crystallised twice from ethanol/water (4:1) to give **7** (21.17 g, 40%). The product was identical to that obtained by procedure **A** from ipriflavone (**1**).

Treatment of 1-(2-Hydroxy-4-isopropoxyphenyl)-2-phenylethanone (7) with Sodium Hydroxide: Compound **7** (2.37 g, 8.8 mmol) was added to a mixture of 2 M NaOH solution (100 mL) and methanol (100 mL) and the mixture was then stirred for 10 d at room temperature. The mixture was neutralised with 5 M HCl and extracted with ethyl acetate. The organic layer was concentrated under vacuum and column-chromatographed on silica gel. The products were eluted with a linear gradient mixture of hexane/CH_2Cl_2 and then CH_2Cl_2/ethyl acetate. The two different products **12** and **13** were isolated.

2-Hydroxy-4-isopropoxybenzoic Acid (12): (300 mg, 17.5%), m.p. 137−138 °C [ref.[56] 142 °C]. − $C_{10}H_{12}O_4$ (196.2): calcd. C 61.2, H 6.2; found C 61.5, H 5.9. − IR: $\tilde{\nu}_{max}$ = 2985, 2935, 2877, 2697, 2556, 1631, 1585, 1503, 1250, 1095. − NMR: δ_H(400 MHz; [D_6]DMSO) = 1.27 [d, 6 H, *J* = 6.0, $(CH_3)_2CHO$], 4.67−4.72 [m, 1 H, $(CH_3)_2CHO$], 6.44 (d, *J* = 2.4 Hz, 1 H, 3-H), 6.45 (dd, *J* = 8.6, *J* = 2.4 Hz, 1 H, 5-H) 7.67 (d, *J* = 8.6 Hz, 1 H, 6-H), 11.50 (1 H, br., OH), 13.51 (1 H, br., OH); δ_C(100 MHz, [D_6]DMSO) = 22.1, 69.1, 101.8, 105.2, 112.6, 131.6, 161.1, 164.3, 173.0.

Benzoic Acid (13): (70 mg, 6.5%), m.p. 120−122 °C (ref.[57] 122.4 °C).

Prolonged Treatment of Ipriflavone (1) with Sodium Hydroxide: Compound **1** (2.45 g, 8.75 mmol) was added to a mixture of 2 M NaOH solution (100 mL) and methanol (100 mL) and the mixture was then stirred for 10 d at room temperature. It was neutralised with 5 M HCl and extracted with ethyl acetate. The organic layer was concentrated in vacuum and column-chromatographed on silica gel. The products were eluted with a linear gradient mixture of hexane/CH_2Cl_2 and then CH_2Cl_2/ethyl acetate. We isolated 1-(2-hydroxy-4-isopropoxyphenyl)-2-phenylethanone (**7**) (0.57 g, 24%), 2-hydroxy-4-isopropoxybenzoic acid (**12**) (0.38 g, 22%) and benzoic acid (**13**) (0.02 g, 1.8%). The products were identical to those obtained earlier.

Treatment of Ipriflavone (1) with Sulfuric Acid: A suspension of **1** (1.0 g, 3.5 mmol) in concentrated H_2SO_4 (8 mL) was stirred at room temperature for 18 h. The reaction mixture was then poured onto ice (50 g). The precipitate was filtered off, and washed with water (200 mL) to give 0.71 g of crude product. After separation by flash column chromatography ($CHCl_3$/ethyl acetate, 9:1), different products were obtained (see also Table 1, sample 1).

7-Hydroxyisoflavone (16): (0.27 g, 32%), m.p. 215−216 °C [ref.[58] 215 °C]. − $C_{18}H_{16}O_3$: calcd. C 75.6, H 4.2; found C 75.5, H 4.0. − UV: λ_{max}(96% ethanol) (log ε) = 242 (4.42), 298 (4.04). − IR: $\tilde{\nu}_{max}$ = 3230, 3050, 2960, 2840, 1625, 1580, 1560, 1500, 1260, 1740, 690. − NMR: δ_H(400 MHz; [D$_6$]DMSO) = 6.93 (d, *J* = 2.2 Hz, 1 H, 8-H), 7.00 (dd, *J* = 8.8, *J* = 2.2 Hz, 1 H, 6-H), 7.54−7.68 (m, 2 H, Ph), 7.41−7.53 (m, 2 H, Ph), 8.03 (d, *J* = 8.8 Hz, 1 H, 5-H), 8.44 (s, 1 H, 2-H), 10.88 (s, 1 H, OH). − MS: *m*/*z* (%) = 238 [M$^+$] (100), 237 (95), 210 (5), 209 (4), 181 (8), 152 (10), 136 (34), 108 (28), 102 (13).

7-Hydroxy-4′-isopropylisoflavone (18): White crystals (0.15 g, 15%), m.p. 213−215 °C. − $C_{18}H_{16}O_3$ (280.3): calcd. C 77.1, H 5.7; found: C 77.1, H 5.6. − IR: $\tilde{\nu}_{max}$ = 3126, 2959, 2938, 2872, 1638, 1621, 1601, 1570, 1515, 1452, 1388, 1314, 1272, 1195, 1100, 1057. − NMR: δ_H(400 MHz; [D$_6$]DMSO) = 1.22 [d, 6 H, *J* = 6.9, (C*H*$_3$)$_2$CH], 2.89−2.95 [m, 1 H, (CH$_3$)$_2$C*H*], 6.88 (d, *J* = 2.2 Hz, 1 H, 8-H), 6.95 (dd, *J* = 8.7, *J* = 2.2 Hz, 1 H, 6-H), 7.27−7.39 (m, 2 H, Ph), 7.41−7.53 (m, 2 H, Ph), 7.97 (d, *J* = 8.7 Hz, 1 H, 5-H), 8.36 (s, 1 H, 2-H), 10.41 (s, 1 H, OH).

7-Hydroxy-2′,5′-diisopropylisoflavone (21): White crystals (30 mg, 3%), m.p. 290−292 °C. − $C_{21}H_{22}O_3$ (322.4): calcd. C 78.2, H 6.9; found C 78.0, H 7.1. − IR: $\tilde{\nu}_{max}$ = 3078, 2955, 2924, 2872, 1625, 1585, 1498, 1450, 1385, 1308, 1286, 1261, 1195, 1099, 1043, 954, 827, 800. − NMR: δ_H(400 MHz; [D$_6$]DMSO) = 1.06 [6 H, br., (C*H*$_3$)$_2$CH], 1.19 [d, 6 H, *J* = 6.1 (C*H*$_3$)$_2$CH], 2.68−2.74 [m, 1 H, (CH$_3$)$_2$C*H*], 2.83−2.89 [m, 1 H, (CH$_3$)$_2$C*H*], 6.88 (d, *J* = 2.1 Hz, 1 H, 8-H), 6.84−7.02 (m, 2 H, 6-H and 6′-H), 7.24 (dd, *J* = 2.0, *J* = 4.1 Hz, 1 H, 4′-H), 7.30 (d, *J* = 4.1 Hz, 1 H, 3′-H), 7.93 (d, *J* = 8.8 Hz, 1 H, 5-H), 8.12 (s, 1 H, 2-H); δ_C(100 MHz; CDCl$_3$) = 24.1 [4 C, (*C*H$_3$)$_2$CH], 30.0 [(CH$_3$)$_2$*C*H], 33.1 [(CH$_3$)$_2$*C*H], 102.4 (C-8), 115.4 (C-6), 116.5 (C-4a), 125.2 (C-3′), 125.4 (C-1′), 126.7 (C-4′), 127.4 (C-5), 128.9 (C-6′), 130.8 (C-3), 145.5 (C-5′), 145.8 (C-2′), 153.8 (C-2), 158.0 (C-8a), 162.9 (C-7), 175.2 (C-4).

7-Hydroxy-3′,5′-diisopropylisoflavone (29): (0.1 g, 9%), m.p. 247−250 °C. − $C_{21}H_{22}O_3$ (322.4): calcd. C 78.2, H 6.9; found C 78.4, H 6.9. − IR: $\tilde{\nu}_{max}$ = 3084, 2959, 2933, 2868, 1626, 1582, 1454, 1388, 1286, 1196, 1100, 954, 875, 819. − NMR: δ_H(400 MHz; [D$_6$]DMSO) = 1.22 [d, 12 H, *J* = 6.9 (C*H*$_3$)$_2$CH], 2.83−2.90 [m, 2 H, (CH$_3$)$_2$C*H*], 6.87 (d, *J* = 2.2 Hz, 1 H, 8-H), 6.95 (dd, *J* = 8.7, *J* = 2.2 Hz, 1 H, 6-H), 7.11 (t, *J* = 1.6 Hz, 1 H, 4′-H), 7.21 (d, *J* = 1.6 Hz, 2 H, 2′-H and 6′-H), 7.97 (d, *J* = 8.7 Hz, 1 H, 5-H), 8.35 (s, 1 H, 2-H), 12.82 (s, 1 H, OH).

Treatment of 7-Hydroxyisoflavone (16) with 2-Propanol in Concentrated H_2SO_4

Method A: A suspension of **16** (1.0 g, 4.2 mmol) and 2-propanol (0.25 g, 0.32 mL, 4.2 mmol) in concentrated H_2SO_4 (10 mL) was stirred at room temperature for 18 h. The reaction mixture was then poured onto ice (50 g). The precipitated crystals were filtered off and washed with water to give 0.92 g of white powder as crude product. After separation by flash column chromatography ($CHCl_3$/ethyl acetate, 9:1), the same compounds **16**, **18**, **21**, and **29** as produced in the previous experiment were obtained (see also Table 1, sample 2).

7-Hydroxyisoflavone (16): Recovered starting material (0.3 g, 30%).

7-Hydroxy-4′-isopropylisoflavone (18): White crystals (0.11 g, 9%). The compound was identical to that obtained in the previous reaction.

7-Hydroxy-2′,5′-diisopropylisoflavone (21): White crystals (85 mg, 6%). The compound was identical to that obtained in the previous reaction.

7-Hydroxy-3′,5′-diisopropyl-isoflavone (29): White crystals (0.11 g, 8%). The compound was identical to that obtained in the previous reaction.

Method B: The same procedure as in Method A was used, except that double the amount of 2-propanol (0.5 g, 0.64 mL, 8.4 mmol) was added. Separation of the crude product mixture (1.05 g) by column chromatography on silica gel or by reverse phase preparative TLC resulted in different products (see also Table 1, sample 3).

7-Hydroxy-4′-isopropylisoflavone (18): White crystals (81 mg, 7%). The compound was identical to that obtained earlier.

7-Hydroxy-2′,5′-diisopropylisoflavone (21): White crystals (0.12 g, 8%). The compound was identical to that obtained earlier.

7-Hydroxy-2′,4′,5′-triisopropylisoflavone (23): (10 mg, 0.6%), m.p. 298−300 °C. − $C_{24}H_{28}O_3$ (364.5): calcd. C 79.1, H 7.7; found C 78.9, H 7.9. − IR: $\tilde{\nu}_{max}$ = 3097, 3015, 3014, 2961, 2916, 2861, 1624, 1583, 1501, 1453, 1381, 1304, 1280, 1232, 1194, 1100, 1082, 1053, 954, 899, 848, 785. − NMR: δ_H(400 MHz; [D$_6$]DMSO) = 1.07−1.11 [m, 6 H, (C*H*$_3$)$_2$CH], 1.17 [d, 6 H, *J* = 6.8, (C*H*$_3$)$_2$CH], 1.23 [d, 6 H, *J* = 6.7, (C*H*$_3$)$_2$CH], 2.63−2.72 [m, 1 H, (CH$_3$)$_2$C*H*], 3.18−3.22 [m, 2 H, (CH$_3$)$_2$C*H*], 6.88 (d, *J* = 2.2 Hz, 1 H, 8-H), 6.92 (s, 1 H, 3′-H), 6.94 (dd, *J* = 8.7 Hz, 1 H, 2.2, 6-H), 7.22 (s, 1 H, 6′-H), 7.93 (d, *J* = 8.8 Hz, 1 H, 5-H), 8.17 (s, 1 H, 2-H), 10.83 (s, 1 H, OH).

7-Hydroxy-3′-isopropyl-6′-sulfonylisoflavone (24): White crystals (30 mg, 2%), m.p. 300−303 °C. − IR: $\tilde{\nu}_{max}$ = 3448, 3186, 3066, 2963, 2872, 1632, 1593, 1461, 1406, 1289, 1195, 1097, 1054, 1016, 826. − NMR: δ_H(400 MHz; [D$_6$]DMSO) = 1.22 [d, 6 H, *J* = 6.9 (C*H*$_3$)$_2$CH], 2.85−2.91 [m, 1 H, (CH$_3$)$_2$C*H*], 6.86 (d, *J* = 2.2 Hz, 1 H, 8-H), 6.91 (dd, *J* = 8.7 Hz, 1 H, 2.2, 6-H), 7.04 (d, *J* = 1.8 Hz, 1 H, 2′-H), 7.19 (dd, *J* = 8.1 Hz, 1 H, 1.8, 4′-H), 7.79 (d, *J* = 8.1 Hz, 1 H, 5′-H), 7.90 (d, *J* = 8.7 Hz, 1 H, 5-H), 8.13 (s, 1 H, OH), ca. 10.5 (1 H, br., OH); δ_C(100 MHz; [D$_6$]DMSO) = 24.0 [2 C, (*C*H$_3$)$_2$CH], 33.3 [(CH$_3$)$_2$*C*H], 102.4 (C-8), 114.9 (C-6), 117.3 (C-4a), 123.5 (C-3), 125.0 (C-4′), 127.4 (C-5), 127.6 (C-5′), 129.5 (C-1′), 130.8 (C-2′), 145.2 (C-6′), 148.3 (C-3′), 154.4 (C-2), 157.7 (C-8a), 162.5 (C-7), 177.4 (C-4).

7-Hydroxy-2′-isopropyl-5′-sulfonylisoflavone (25) and 7-Hydroxy-3′-isopropyl-4′-sulfonylisoflavone (26): 10 mg of a ca. 1:1 mixture. − IR (neat): $\tilde{\nu}_{max}$ = 3448, 3084, 2963, 2923, 2853, 1730, 1624, 1588, 1466, 1384, 1258, 1183, 1081, 1023, 826. − NMR: **25**: δ_H(400 MHz; [D$_6$]DMSO) = 1.07−1.28 [m, 6 H, (C*H*$_3$)$_2$CH], 2.71−2.78 [m, 1 H, (CH$_3$)$_2$C*H*], 6.91 (d, *J* = 2.2 Hz, 1 H, 8-H), 6.95 (dd, *J* = 2.2, *J* = 8.7 Hz, 1 H, 6-H), 7.34 (d, *J* = 1.8 Hz, 1 H, 6′-H), 7.35 (d, *J* = 8.5 Hz, 1 H, 3′-H), 7.61 (dd, *J* = 1.8, *J* = 8.5 Hz, 1 H, 4′-H), 7.95 (d, *J* = 8.7 Hz, 1 H, 5-H), 8.20 (s, 1 H, 2-H), 10.8 (1 H, br., OH); **26**: δ_H(400 MHz; [D$_6$]DMSO) = 1.07−1.28 [m, 6 H, (C*H*$_3$)$_2$CH], 4.11−4.17 [m, 1 H, (CH$_3$)$_2$C*H*], 6.89 (d, *J* = 2.2 Hz, 1 H, 8-H), 6.95 (dd, *J* = 2.2, *J* = 8.7 Hz, 1 H, 6-H), 7.27 (dd, *J* = 1.7, *J* = 8.0 Hz, 1 H, 6′-H), 7.52 (d, *J* = 1.7 Hz, 1 H, 2′-H), 7.78 (d, *J* = 8.0 Hz, 1 H, 4′-H), 7.99 (d, *J* = 8.7 Hz, 1 H, 5-H), 8.37 (s, 1 H, 2-H), 10.8 (1 H, br., OH); **25**: δ_C(100 MHz; [D$_6$]DMSO) = 24.3

[(CH_3)$_2$CH], 30.3 [(CH_3)$_2$*C*H], 102.4 (C-8), 115.5 (C-6), 116.6 (C-4a), 124.8 (C-3′), 125.1 (C-3), 126.2 (C-4′), 127.6 (C-5), 128.2 (C-6′), 130.3 (C-1′), 145.8 (C-5′), 148.9 (C-2′), 154.1 (C-2), 158.1 (C-8a), 163.0 (C-7), 175.1 (C-4); **26**: δ_C(100 MHz; [D$_6$]DMSO) = 24.3 [(*C*H$_3$)$_2$CH], 28.3 [(CH$_3$)$_2$*C*H], 102.6 (C-8), 115.5 (C-6), 117.0 (C-4a), 123.7 (C-3), 125.2 (C-6′), 126.7 (C-5′), 127.0 (C-2′), 127.5 (C-5), 132.8 (C-1′), 145.2 (C-4′), 146.6 (C-3′), 154.1 (C-2), 157.7 (C-8a), 162.9 (C-7), 174.7 (C-4).

7-Hydroxy-3′,4′-diisopropyl-6′-sulfonylisoflavone (27): White crystals (30 mg, 2%), m.p. 283−286 °C. − $C_{21}H_{22}O_6S$ (402.5): calcd. C 62.7, H 5.5; found C 62.6, H 5.2. − IR: $\tilde{\nu}_{max}$ = 3078, 3039, 2964, 2925, 2859, 1648, 1629, 1560, 1461, 1409, 1305, 1280, 1219, 1197, 1175, 1139, 1127, 1098, 1070, 1044, 844, 789, 683. − NMR: δ_H(400 MHz; CDCl$_3$ + [D$_6$]DMSO) = 1.15 [d, 6 H, *J* = 6.8, (C*H*$_3$)$_2$CH], 1.18 [d, 6 H, *J* = 6.8, (C*H*$_3$)$_2$CH], 3.17−3.24 [m, 2 H, (CH$_3$)$_2$C*H*], 6.74 (d, *J* = 2.0 Hz, 1 H, 8-H), 6.80 (dd, *J* = 8.8 Hz, 1 H, 2.2, 6-H), 7.04 (s, 1 H, 2′-H), 7.91 (s, 1 H, 5′-H), 7.92 (d, *J* = 8.8 Hz, 1 H, 5-H), 8.05 (s, 1 H, 2-H), 10.23 (1 H, br., OH); δ_C(100 MHz; CDCl$_3$ + [D$_6$]DMSO) = 23.8 [4 C, (*C*H$_3$)$_2$CH], 32.0 [(CH$_3$)$_2$*C*H], 102.1 (C-8), 114.9 (C-6), 116.7 (C-4a), 124.4 (C-3), 124.8 (C-5′), 126.6 (C-1′), 127.5 (C-5), 129.3 (C-2′), 142.9 (C-6′), 144.7 (C-4′), 146.3 (C-3′), 154.3 (C-2), 158.0 (C-8a), 162.8 (C-7), 176.5 (C-4).

7-Hydroxy-2′,4′-diisopropyl-5′-sulfonylisoflavone (28): White crystals (50 mg, 3%), m.p. 287−290 °C. − IR: $\tilde{\nu}_{max}$ = 2427, 3199, 3060, 2962, 2922, 2870, 1625, 1595, 1457, 1183, 1100, 1073, 1025, 955, 896, 848. − NMR: δ_H(400 MHz; [D$_6$]DMSO) = 1.06 [6 H, br., (C*H*$_3$)$_2$CH], 1.18 [6 H, br., *J* = 6.8, (C*H*$_3$)$_2$CH], 2.68−2.73 [m, 1 H, (CH$_3$)$_2$C*H*], 4.15 [m, 1 H, (CH$_3$)$_2$C*H*], 6.90 (d, *J* = 2.2 Hz, 1 H, 8-H), 6.93 (dd, *J* = 8.7, *J* = 2.2 Hz, 1 H, 6-H), 7.29 (s, 1 H, 3′-H), 7.45 (s, 1 H, 6′-H), 7.94 (d, *J* = 8.7 Hz, 1 H, 5-H), 8.19 (s, 1 H, 2-H); δ_C(100 MHz; [D$_6$]DMSO) = 24.3 [4 C, (*C*H$_3$)$_2$CH], 28.4 [(CH$_3$)$_2$*C*H], 30.5 [(CH$_3$)$_2$*C*H], 102.6 (C-8), 115.6 (C-6), 116.6 (C-4a), 123.0 (C-3′), 125.1 (C-3), 127.3 (C-1′), 127.6 (C-5), 129.4 (C-6′), 142.8 (C5′), 147.1 (C-4′), 149.2 (C-2′), 154.0 (C-2), 158.2 (C-8a), 163.1 (C-7), 175.4 (C-4).

7-Hydroxy-3′,5′-diisopropylisoflavone (29): White crystals (60 mg, 4%). The compound was identical to that obtained earlier.

7-Hydroxy-3′,5′,8-triisopropylisoflavone (30): Pale yellow gum (5 mg, 0.3%). − IR (neat): $\tilde{\nu}_{max}$ = 3211, 3071, 2960, 2934, 2877, 1627, 1588, 1429, 1387, 1279, 1188, 1089, 956, 876, 796. − NMR: δ_H(400 MHz; CDCl$_3$) = 1.29 [d, 12 H, *J* = 6.9 (C*H*$_3$)$_2$CH], 1.42 [d, 6 H, *J* = 6.9 (C*H*$_3$)$_2$CH], 2.91−3.02 [m, 2 H, (CH$_3$)$_2$C*H*], 3.76 [m, 1 H, (CH$_3$)$_2$C*H*], 7.02 (d, *J* = 8.8 Hz, 1 H, 6-H), 7.13 (s, 1 H, 4′-H), 7.26 (s, 2 H, 2′,6′-H), 8.01 (d, *J* = 8.8 Hz, 1 H, 5-H), 8.09 (s, 1 H, 2-H)- 8.71 (1 H, br., OH); δ_C(100 MHz; CDCl$_3$) = 20.5 [(*C*H$_3$)$_2$CH], 24.0 [2 C, (*C*H$_3$)$_2$CH], 24.1 [(CH$_3$)$_2$*C*H], 34.2 [2 C, (CH$_3$)$_2$*C*H], 115.7 (C-6), 117.7 (C-4a), 121.1 (C-8), 124.6 (C-4′), 124.8 (2 C, C-2′,6′), 124.9 (C-5), 131.6 (C-1′), 149.0 (2 C, C-3′,5′), 153.1 (C-2), 156.4 (C-8a), 160.2 (C-7), 177.4 (C-4). − FABMS found 365.2117 [MH$^+$], $C_{24}H_{28}O_3$ requires 365.2099 [MH$^+$].

7-Hydroxy-3′,4′,8-triisopropylisoflavone (31): Pale yellow gum (5 mg, 0.3%). − IR (neat): $\tilde{\nu}_{max}$ = 3219, 3064, 3020, 2960, 2933, 2875, 1625, 1593, 1496, 1429, 1385, 1283, 1187, 993, 832, 799. − NMR: δ_H(400 MHz; CDCl$_3$) = 1.24 [d, 6 H, *J* = 6.9, (C*H*$_3$)$_2$CH], 1.29 [d, 6 H, *J* = 6.9, (C*H*$_3$)$_2$CH], 1.43 [d, 6 H, *J* = 7.1, (C*H*$_3$)$_2$CH], 2.82−2.89 [m, 2 H, (CH$_3$)$_2$C*H*], 3.71−3.76 [m, 1 H, (CH$_3$)$_2$C*H*], 6.87 (d, *J* = 2.2 Hz, 1 H, 8-H), 6.85 (dd, *J* = 8.7, *J* = 2.2 Hz, 1 H, 6-H), 7.00 (d, *J* = 1.8 Hz, 1 H, 2′-H), 7.24 (dd, *J* = 8.1, *J* = 1.8 Hz, 1 H, 6′-H), 7.33 (d, *J* = 8.1 Hz, 1 H, 5′-H), 7.87 (s, 1 H, 2-H), 8.00 (d, *J* = 8.7 Hz, 1 H, 5-H);.

7-Hydroxy-2′,4′,5′,8-tetraisopropylisoflavone (32): Pale yellow gum (10 mg, 0.5%). − IR: $\tilde{\nu}_{max}$ = 3296, 3035, 2963, 2927, 2870, 1725, 1630, 1588, 1502, 1429, 1384, 1263, 1087, 1019, 799. − NMR: δ_H(400 MHz; CDCl$_3$) = 1.22 [d, 6 H, *J* = 6.8, (C*H*$_3$)$_2$CH], 1.27 [d, 12 H, *J* = 6.9, (C*H*$_3$)$_2$CH], 1.44 [d, 6 H, *J* = 6.4, (C*H*$_3$)$_2$CH], 2.83−2.89 [m, 1 H, (CH$_3$)$_2$C*H*], 3.21−3.29 [m, 2 H, (CH$_3$)$_2$C*H*], 3.73−3.79 [m, 1 H, (CH$_3$)$_2$C*H*], 6.06 (1 H, br., OH), 6.83 (d, *J* = 8.7 Hz, 1 H, 6-H), 6.97 (s, 1 H, 3′-H), 7.26 (s, 1 H, 6′-H), 7.85 (s, 1 H, 2-H), 8.03 (d, *J* = 8.7 Hz, 1 H, 5-H). − FAB MS found 407.2586 [MH$^+$], $C_{27}H_{34}O_3$ requires 407.2566 [MH$^+$].

Oxidation of Ipriflavone (1) under Basic Conditions: ***Caution:*** *During the workup of a reaction mixture, after treatment of the excess H_2O_2 with $NaHSO_3$ and extraction of the product with ethyl acetate, a severe explosion occurred during the evaporation of the solvent in vacuum!* Compound **1** (12.0 g, 42.9 mmol) was dissolved in a mixture of 1 M NaOH solution (6.0 mL) and acetone (300 mL). A 30% solution of H_2O_2 (60 mL) was added dropwise to the cooled mixture, which then was stirred for 10 h at room temperature. The suspension was subsequently kept in an open dish for 24 h. The white crystals that separated were filtered off, washed with acetone (10 mL) and dried to give 2,3-epoxy-7-isopropoxyisoflavanone (**33**) (11.9 g, 95%), m.p. 106−108 °C. − $C_{18}H_{16}O_4$ (296.3): calcd. C 73.0, H 5.4; found C 73.1, H 5.2. − UV: λ_{max}(96% ethanol) (log ε) = 216 (4.40), 233 (3.91), 281 (4.19). − IR: $\tilde{\nu}_{max}$ = 3085, 3035, 2980, 2926, 2875, 1669, 1620, 1569, 1245, 1114, 1024, 875, 751, 694. − NMR: δ_H(400 MHz; CDCl$_3$) = 1.38 [d, 6 H, *J* = 6.0 (C*H*$_3$)$_2$CHO], 4.60−4.66 [m, 1 H, (CH$_3$)$_2$C*H*O], 5.47 (s, 1 H, 2-H), 5.54 (d, *J* = 2.3 Hz, 1 H, 8-H), 6.73 (dd, *J* = 2.3, *J* = 8.8 Hz, 1 H, 6-H), 7.4−7.5 (m, 5 H, Ph), 7.96 (d, *J* = 8.8 Hz, 1 H, 5-H); δ_C(100 MHz; CDCl$_3$) = 21.6 [2 C, (*C*H$_3$)$_2$CHO], 62.1 (C-3), 70.6 [(CH$_3$)$_2$*C*HO], 83.1 (C-2), 102.2 (C-8), 112.5 (C-6), 113.0 (C-10), 127.1 (2 C, C-2′,6′), 128.1 (2 C, C-3′,5′), 128.7 (C-4′), 129.2 (C-5), 130.7 (C-1′), 157.0 (C-9), 164.6 (C-10) and 185.8 (C-4). − MS: *m*/*z* (%) = 296 [M$^+$] (15), 268 (23), 267 (14), 254 (18), 237 (13), 226 (70), 225 (32), 197 (62), 191 (10), 168 (10), 137 (33), 120 (30), 105 (100), 77 (38), 63(24).

Crystal Data for $C_{18}H_{16}O_4$: *M* = 296.32, triclinic, *a* = 7.198(1), *b* = 15.734(3), *c* = 6.894(1) Å, α = 97.80(1), β = 109.12(1), γ = 79.73(1)°, *V* = 723.3(2) Å^3, space group $P\bar{1}$, *Z* = 2, μ(Cu-K_λ) = 0.788 mm^{-1}, 3117 reflections measured 2866 unique (R_{int} = 0.036). The final *R*(*F*) was 0.042 [1577 reflections $I > 2\sigma(I)$] (see also ref.[42]).

Treatment of 2,3-Epoxy-7-isopropoxyisoflavanone (33) with Sodium Hydroxide: Compound **33** (2.0 g, 6.7 mmol) was added to a mixture of 0.2 M NaOH solution (50 mL) and acetone (25 mL), after which the mixture was stirred for 2 weeks, and then neutralised with 2 M HCl and the solvents evaporated. The organic residue was extracted with ethyl acetate (2 × 10 mL). The concentrated extract was purified on silica gel by column chromatography with hexane/ethyl acetate (8:2). The first of two collected fractions was the recovered starting material **33** (1.2 g, 60%). The second fraction was concentrated and the residue was crystallised from hexane to give 3-hydroxy-2-(2-hydroxy-4-isopropoxybenzoyl)-7-isopropoxy-2-phenylisoflavanone (**40**) (0.12 g; 16% based on the recovered starting material), m.p. 212−217 °C. − $C_{34}H_{32}O_7$ (552.6): calcd. C 73.9, H 5.8; found C 73.7, H 6.0. − IR: $\tilde{\nu}_{max}$ = 3527, 3064, 2973, 2934, 1696, 1607, 1567, 1266, 1167, 1109, 726, 698. − NMR: δ_H(400 MHz; CDCl$_3$) = 1.24, 1.38 [d, 6 H, *J* = 6.0, (C*H*$_3$)$_2$CHO], 1.26 [d, 6 H, *J* = 6.0, (C*H*$_3$)$_2$CHO], 4.49−4.54 [m, 2 H, (CH$_3$)$_2$C*H*O], 4.56 (1 H, br., 3-OH), 6.09, 6.67 (dd, 2 H, *J* = 9.4, *J* = 2.5, *J* = 8.8, *J* = 2.3 Hz, 6-H, 5′′′-H), 6.23, 6.32 (d, 2 H, *J* = 2.5, *J* = 2.3 Hz, 8-H, 3′′′-H), 6.80−7.30 [m, 10 H, 2 × Ph (2′,6′-H; 2′′,6′′-H)], 7.60, 7.97 (d, 2 H, *J* = 9.4, *J* = 8.8 Hz, 5-H, 6′′′-H), 12.03 (s, 1 H, 2′′′-OH); δ_C(100 MHz; CDCl$_3$) = 21.5, 21.7,

22.0 [2 × (CH_3)$_2$CHO], 70.5, 70.7 [2 × (CH_3)$_2$*C*HO], 80.6 (C-3), 92.6 (C-2), 101.6, 103.2 (C-7, C-3′′′), 109.9, 112.2 (C-6, C-5′′′), 110.4, 115.4 (C-5, C-1′′′), 126.5, 127.2, 127.3, 127.5 (C-2′, C-6′; C-3′, C-5′; C-2′′, C-6′′; C-3′′, C-5′′), 127.8, 128.4 (C-4′, C-4′′), 129.5, 134.3 (C-5, C-6′′′), 134.8, 136.2 (C-1′, C-1′′), 160.4, 164.9, 165.0, 167.8 (C-7, C-8a, C-2′′′, C-4′′′), 192.9, 201.7 (2 × C=O). − MS: *m*/*z* (%) = 552 [MH^+] (2.3), 447 (1.5), 373 (3.5), 356 (4.6), 313 (3.5), 268 (15), 226 (17), 179 (56), 137 (100). − Only one set of signals was detected in the ^{1}H and ^{13}C NMR spectra. This observation led us to the conclusion that only one diastereomer had been formed during the reaction.

Crystal Data for $C_{34}H_{32}O_7$: M = 552.59, monoclinic, a = 9.517(5), b = 13.281(5), c = 23.631(5) Å, β = 101.008(5)°, V = 2932(2) Å^3, space group $P2_1$, Z = 4, μ(Cu-K_λ) = 0.681 mm^{-1}, 6420 reflections measured 6408 unique (R_{int} = 0.0794). The final $R(F)$ was 0.2202 [5951 reflections $I > 2\sigma(I)$] (see also ref.[42]). − On the basis of the XRD data the obtained diastereomer has the following configuration: (2*S*,3*S*) or (2*R*,3*R*).

Oxidation of Ipriflavone (1) under Acidic Conditions: Compound **1** (10.0 g, 35.7 mmol), acetonitrile (20 mL), acetic acid (96%, 20 mL), and water (60 mL) were mixed and refluxed for 40 h with 30% H_2O_2 (27 mL), which was added in 3 portions at 8 h intervals. Water (40 mL) was added, the organic solvent was removed under reduced pressure and the residue was extracted with CH_2Cl_2 (3 × 50 mL). The organic layer was dried with Na_2SO_4, filtered, and the solvents evaporated. The residue was chromatographed on Kieselgel 60 with hexane/$CHCl_3$ (1:1), $CHCl_3$, CH_2Cl_2/ethyl acetate (6:1), ethyl acetate, and ethanol to give different products.

Ipriflavone (1): Recovered starting material (7.8 g, 78%).

2-Hydroxy-4-isopropoxybenzoic Acid (12): The compound was identical to that obtained earlier (110 mg, 1.5%).

Benzoic Acid (13): The compound was identical to that obtained earlier (110 mg, 2.5%).

8-Hydroxy-7-isopropoxy-isoflavone (42): 30 mg, 0.3%, m.p. 196−205 °C. − $C_{18}H_{16}O_4$ (296.3): calcd. C 73.0, H 5.4; found: calcd. C 73.2, H 5.5. − IR: $\tilde{\nu}_{max}$ = 3265, 3061, 2976, 2933, 1624, 1591, 1565, 1505, 1392, 1257, 1111, 1043, 889, 784. − NMR: δ_H(400 MHz, [D$_6$]DMSO) = 1.32 [d, 6 H, J = 6.0, (CH_3)$_2$CHO], 4.74−4.51 [m, 1 H, (CH_3)$_2$C*H*O], 7.21 (d, J = 9.2 Hz, 1 H, 6-H), 7.38−7.46 (m, 3 H, Ph), 7.56−7.59 (m, 3 H, Ph), 8.48 (s, 1 H, 2-H), 9.45 (s, 1 H, OH); δ_C(100 MHz, [D$_6$]DMSO) = 22.1 [(CH_3)$_2$CHO], 71.8 [(CH_3)$_2$*C*HO], 113.4 (C-6), 115.5 (C-5), 118.8 (C-4a), 123.4 (C-3), 128.0 (C-4′), 128.4 (C-3′, C-5′), 129.3 (C-2′, C-6′), 135.9 (C-8), 146.4 (C-7), 149.7 (C-7a), 154.2 (C-2), 175.2 (C=O).

2,3-Dihydroxy-7-isopropoxyisoflavanone (43): 44:56 mixture of two diastereomers (320 mg, 2.5%), m.p. 113−118 °C. − $C_{18}H_{18}O_5$ (314.3): calcd. C 68.8, H 5.8; found C 68.4, H 6.0. − IR: $\tilde{\nu}_{max}$ = 3493, 3303, 3071, 2991, 2969, 2926, 1669, 1676, 1610, 1574, 1500, 1440, 1250, 1193, 1149, 1101, 1077, 1021, 838, 701. − NMR: Major component: δ_H(400 MHz; [D$_6$]DMSO) = 1.27 [d, 6 H, J = 6.0, (CH_3)$_2$CHO], 4.64−4.69 [m, 1 H, (CH_3)$_2$C*H*O], 5.77 (d, J = 5.0 Hz, 1 H, 2-OH), 5.98 (s, 1 H, 3-OH), 6.42 (d, J = 2.3 Hz, 1 H, 8-H), 6.62 (dd, J = 2.3, J = 8.8 Hz, 1 H, 6-H), 7.26−7.32 (m, 3 H, Ph), 7.38 (dd, 2 H, J = 1.8, J = 8.1, Ph), 7.70 (d, J = 8.8 Hz, 1 H, 5-H), 7.79 (d, J = 5.0 Hz, 1 H, 2-H); minor component: δ_H(400 MHz; [D$_6$]DMSO) = 1.29 [d, 6 H, J = 6.0, (CH_3)$_2$CHO], 4.71−4.77 [m, 1 H, (CH_3)$_2$C*H*O], 5.40 (d, J = 5.2 Hz, 1 H, 2-OH), 6.49 (s, 1 H, 3-OH), 6.53 (d, J = 2.3 Hz, 1 H, 8-H), 6.64 (dd, J = 2.3, J = 8.8 Hz, 1 H, 6-H), 7.26−7.32 (m, 3 H, Ph), 7.45 (dd, 2 H, J = 1.5, J = 8.0, Ph), 7.72 (d, J = 8.8 Hz, 1 H, 5-H), 7.80 (d, J = 5.2 Hz, 1 H, 2-H); Major component: δ_C(100 MHz, [D$_6$]DMSO) = 21.9 [(CH_3)$_2$CH], 70.4 [(CH_3)$_2$*C*H], 78.0 (C-3), 99.9 (C-2), 103.1 (C-8), 110.6 (C-6), 114.6 (C-4a), 126.9 (Ph), 127.4 (C-5), 128.2 (Ph), 128.4 (Ph), 139.8 (C-1′), 159.5 (C-8a), 164.5 (C-7), 192.7 (C-4); minor component: δ_C(100 MHz, [D$_6$]DMSO) = 22.0 [(CH_3)$_2$CH], 70.30 [(CH_3)$_2$*C*H], 77.1 (C-3), 100.2 (C-2), 102.8 (C-8), 110.9 (C-6), 113.7 (C-4a), 127.4 (Ph), 127.6 (C-5), 128.3 (Ph), 129.1 (Ph), 138.3 (C-1′), 160.1 (C-8a), 164.5 (C-7), 193.3 (C-4).

Irradiation of Ipriflavone (1): A solution of **1** (0.5 g, 1.8 mmol) in methanol (150 mL) was irradiated for 60 h with a 125-W medium-pressure mercury lamp through a water-cooled immersion jacket made of quartz (no inert gas). [The reaction was monitored by HPLC (see Figure 3).] The reaction mixture was concentrated under vacuum. The residue was dissolved in CH_2Cl_2 (2 mL) and mixed with intensive stirring with petroleum ether (20 mL) for 10 min. The organic layer was decanted and the procedure was repeated twice to give a polymeric residue (**48**, 0.2 g), no definite melting point (found: C 53.7, H 5.4). − IR (neat): $\tilde{\nu}_{max}$ = 3435, 2981, 1740, 1611, 1443, 1253, 764, 702. − NMR: δ_H(400 MHz, $CDCl_3$) = 1.2−1.4 (br), 3.4−3.5 (br), 3.7−3.9 (br), 7.2−7.5 (br). − TLC on SiO_2: multicomponent mixture in different solvent mixtures. − LC-MS: molecular type ions between 311 and 823. − The combined organic layers from the above procedure were concentrated and the residue was chromatographed on silica gel. A rough separation was achieved by "dry column" flash chromatography[59] (elution first with CH_2Cl_2/*n*-hexane, 1:1 and then with CH_2Cl_2/methanol, 9:1). Final purification was achieved by preparative layer chromatography, using different solvent mixtures.

Methyl 2-Hydroxy-4-isopropoxybenzoate (46): R_f = 0.57 [CH_2Cl_2/ethanol (95:5)] (32 mg, 8.5%), white needles, m.p. 45−47 °C [ref.[56] bp_{15} 156−157 °C]. − $C_{11}H_{14}O_4$ (210.2): calcd. C 62.85, H 6.7; found C 63.1, H 7.0. − IR: $\tilde{\nu}_{max}$ = 3085, 2973, 2927, 1667, 1625, 1582, 1503, 1446, 1350, 1331, 1299, 1255, 1193. − NMR: δ_H(400 MHz, $CDCl_3$) = 1.36 [d, 6 H, J = 6.0, (CH_3)$_2$CHO], 3.92 (s, 3 H, Me), 4.56−4.61 [m, 1 H, (CH_3)$_2$C*H*O], 6.40−6.45 (m, 2 H, 3-H and 5-H), 7.72 (d, J = 8.8 Hz, 1 H, 6-H), 10.95 (s, 1 H, 2-OH).

2-Hydroxy-4-isopropoxybenzoic Acid (12): R_f = 0.16 [CH_2Cl_2/ethanol (95:5)] (102 mg, 29.6%), white needles. The compound was identical to that obtained by alkaline hydrolysis of **1**.

Esterification of 2-Hydroxy-4-isopropoxybenzoic Acid (12): A solution of **12** (80 mg, 0.4 mmol) in methanol (2 mL) was refluxed with 20% HCl solution in diethyl ether (2 mL) for 50 h. The solution was evaporated to dryness in vacuum, and the residue was mixed with water (4 mL), neutralised with 20% NaOH (to pH = 8), and extracted with diethyl ether (3 × 5 mL). The combined organic extracts were dried with $MgSO_4$ and filtered, and the solvent was evaporated to give white needles of methyl 2-hydroxy-4-isopropoxybenzoate (**46**) (75 mg, 88%). The product was identical to that obtained by irradiation.

Acknowledgments

The authors thank Tamás Nusser for performing and interpreting the quantum chemical calculations, Felix Hajdú for the analytical HPLC determinations, and János Brlik for the exact mass determinations.

[1] L. Feuer, M. Nógrádi, Á. Gottsegen, B. Vermes, J. Streliszky, A. Wolfner, L. Farkas, S. Antus, M. Kovács, Ger. Pat., 2,125,245, **1971**; *Chem. Abstr.* **1971**, *76*, 72407.

[2] A special issue (Ed.: I. Hermecz) by different authors was dedicated to ipriflavone in *Acta Pharm. Hung.* **1995**, *65*, 6.
[3] J. Y. L. Reginster, *Bone Miner.* **1993**, *23*, 223−232.
[4] P. C. Ruenitz, *Curr. Med. Chem.* **1995**, *2*, 791−802.
[5] I. Dwivedy, S. Ray, *Progress Drug Res.* **1995**, *45*, 289−338 and citations therein.
[6] E. J. Lien, A. Das, L. L. Lien, *Progress Drug Res.* **1996**, *46*, 263−280.
[7] M. Zsuga, T. Nagy, V. Szabó, *Magy. Kém. Foly.* **1980**, *86*, 108−110 and citations therein.
[8] A. I. Tolmatsev, L. M. Shulezhko, A. A. Kisilenko, *Zh. Obsch. Khim.* **1965**, *35*, 1707−1713.
[9] V. V. Mezherickii, G. N. Dorofeenko, *Zh. Obsch. Khim.* **1970**, *40*, 2459−2461.
[10] W. B. Walley, G. Lloyd, *J. Chem. Soc.* **1956**, 3213−3224.
[11] A. I. Virtanen, P. K. Hietala, *Acta Chem. Scand.* **1958**, *12*, 579−580.
[12] J. L. Bose, S. Siddiqui, *J. Sci. Ind. Res.* **1951**, *10B*, 291−294.
[13] R. B. Bradbury, D. E. White, *J. Chem. Soc.* **1951**, 3447−3449.
[14] V. B. Mahesh, N. Narasimhachari, T. R. Seshadri, *Proc. Ind. Acad. Sci., Sect. A* **1954**, *39*, 165−175.
[15] A. Gilbert, A. McGookin, A. Robertson, *J. Chem. Soc.* **1957**, 3740−3745.
[16] R. Iengar, A. C. Mehta, T. R. Seshadri, S. Varadarajan, *J. Sci. Ind. Res.* **1954**, *13B*, 166−174.
[17] A. Robertson, C. W. Suckling, W. B. Whalley, *J. Chem. Soc.* **1949**, 1571−1578.
[18] F. E. King, K. G. Neill, *J. Chem. Soc.* **1952**, 4752−4756.
[19] P. Crabbe, P. R. Leming, C. Djerassi, *J. Am. Chem. Soc.* **1958**, *80*, 5258−5263.
[20] L. H. Briggs, B. F. Cain, *Tetrahedron* **1959**, *6*, 143−144.
[21] A. B. Sahasrabudhe, B. V. Bapat, S. N. Sheshgiri, *Ind. J. Chem. Sect. B* **1982**, *6*, 495−496.
[22] S. W. Banks, P. M. Dewick, *Pytochemistry* **1983**, *22*, 2729−2733.
[23] W. Baker, D. F. Downing, A. J. Floyd, B. Gilbert, W. D. Ollis, R. C. Russell, *J. Chem. Soc.* **1970**, 1219−1223.
[24] T. B. H. McMurry, C. Y. Theng, *J. Chem. Soc.* **1960**, 1491−1498.
[25] M. Zsuga, A. Kiss, *Acta Chim. Hung.* **1987**, *124*, 485−489.
[26] U. Willeke, K. M. Weltring, W. Barz, H. D. VanEtten, *Phytochemistry* **1983**, *22*, 1539−1541.
[27] G. Zemplén, R. Bognár, L. Farkas, *Ber. Dtsch. Chem. Ges.* **1943**, *76*, 267−272.
[28] V. K. Agarwal, R. K. Thappa, S. G. Agarwal, M. S. Mehra, N. S. P. Rao, *Phytochemistry* **1984**, *23*, 2703−2704.
[29] M. L. Sethi, S. C. Taneja, K. L. Dhar, C. K. Atal, *Phytochemistry* **1981**, *20*, 341−342
[30] M. L. Wolfrom, A. S. Gregory, *J. Am. Chem. Soc.* **1940**, *62*, 651−652.
[31] M. L. Wolfrom, A. S. Gregory, *J. Am. Chem. Soc.* **1941**, *63*, 3356−3358.
[32] W. Adam, J. Jekõ, A. Lévai, C. Nemes, T. Patonay, *Liebigs Ann.* **1995**, 1547−1549.
[33] J. A. Donnelly, J. R. Keegan, K. Quigley, *Tetrahedron* **1980**, *36*, 1671−1680.
[34] W. Adam, L. Hadjiarapoglou, A. Lévai, *Synthesis* **1992**, 436−438.
[35] B. C. B. Bezuidenhoudt, E. V. Brandt, D. Ferreira, *J. Chem. Soc., Perkin Trans. 1* **1987**, 1081−1087.
[36] E. Chapman, H. Stephen, *J. Chem. Soc.* **1923**, *123*, 404−409.
[37] W. Baker, *J. Chem. Soc.* **1933**, 1381−1389.
[38] M. L. Wolfrom, J. E. Mahan, P. W. Morgan, G. F. Johnson, *J. Am. Chem. Soc.* **1948**, *63*, 1248−1259.
[39] M. J. S. Dewar, E. G. Zoebish, E. F. Healy, J. J. P. Stewart, *J. Am. Chem. Soc.* **1985**, *107*, 3902−3909.
[40] D. Marx, M. Parrinello, *Nature* **1995**, *375*, 216−218 and citations therein.
[41] D. V. Joshi, J. R. Merchant, R. C. Shah, *J. Org. Chem.* **1956**, *21*, 1104−1109.
[42] Crystallographic data (excluding structure factors) for the structure(s) reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-154798 and -154799. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].
[43] W. Adam, R. Curci, J. O. Edwards, *Acc. Chem. Res.* **1989**, *22*, 205−211.
[44] W. Adam, J. Bialis, L. Hadjiarapoglou, *Chem. Ber.* **1991**, *124*, 2377−2377.
[45] W. Adam, L. Hadjiarapoglou, A. Smerz, *Chem. Ber.* **1991**, *124*, 227−232.
[46] R. W. Murray, R. Jeyaraman, *J. Org. Chem.* **1985**, *50*, 2847.
[47] R. Wolffenstein, *Ber. Dtsch. Chem. Ges.* **1895**, *28*, 2265−2269.
[48] A. Baeyer, V. Villiger, *Ber. Dtsch. Chem. Ges.* **1899**, *32*, 3625−3633.
[49] A. Baeyer, V. Villiger, *Ber. Dtsch. Chem. Ges.* **1900**, *33*, 858−864.
[50] B. C. B. Bezuidenhoudt, E. V. Brandt, J. A. Steenkamp, D. G. Roux, D. Ferreira, *J. Chem. Soc., Perkin Trans. 1* **1988**, 1227−1235.
[51] E. V. Brandt, B. C. B. Bezuidenhoudt, D. G. Roux, *J. Chem. Soc., Chem. Commun.* **1982**, 1409−1410.
[52] B. C. B. Bezuidenhoudt, E. V. Brandt, D. G. Roux, *J. Chem. Soc., Perkin Trans. 1* **1984**, 2767−2778.
[53] Y. Karton, J. Jiang, X. Ji, N. Melman, M. E. Olah, G. L. Stiles, K. A. Jacobsen, *J. Med. Chem.* **1996**, *39*, 2293−2301.
[54] N. Narashimhachasi, L. Ramachandra Row, T. R. Seshadri, *Proc. Indian Acad. Sci., Sect. A* **1952**, *35*, 46−52.
[55] L. Feuer, L. Farkas, M. Nógrádi, J. Strelisky, B. Vermes, A. Wolfner, FR 2,162,175, **1973**; *Chem. Abstr.* **1974**, *80*, 26952; see also: Hung. Pat. 168,744, **1971**.
[56] Ng. T. Thu-Cuc, Ng. Ph. Buu-Hoï, Ng. D. Xuong, *J. Med. Pharm. Chem.* **1961**, *3*, 361−367.
[57] *Lange's Handbook of Chemistry* (Ed.: J. A. Dean), 11th ed., McGraw-Hill Book Company, **1973**, pp. 7−96.
[58] H. S. Mahal, H. S. Rai, K. Venkataraman, *J. Chem. Soc.* **1934**, 1120−1122.
[59] L. M. Harwood, *Aldrichim. Acta* **1985**, *18*, 25.

Received December 18, 2000
[O00646]