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NEW PROCEDURES FOR THE PREPARATION OF ISOFLAVONES WITH UNSUBSTITUTED RING A

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Abstract: Isoflavones with unsubstituted ring A have been synthesized either by the ring closure of 2-hydroxydeoxybenzoins or by the dehydroxylation of 7-hydroxyisoflavones. 7-Mercaptoisoflavones have also been prepared.

Naturally occurring isoflavones are generally substituted both in their rings A and B and the availability of representatives substituted only in ring B is not of importance in this respect. However, the studies of their electronic structure and spectral properties require isoflavones unsubstituted in ring A as well.

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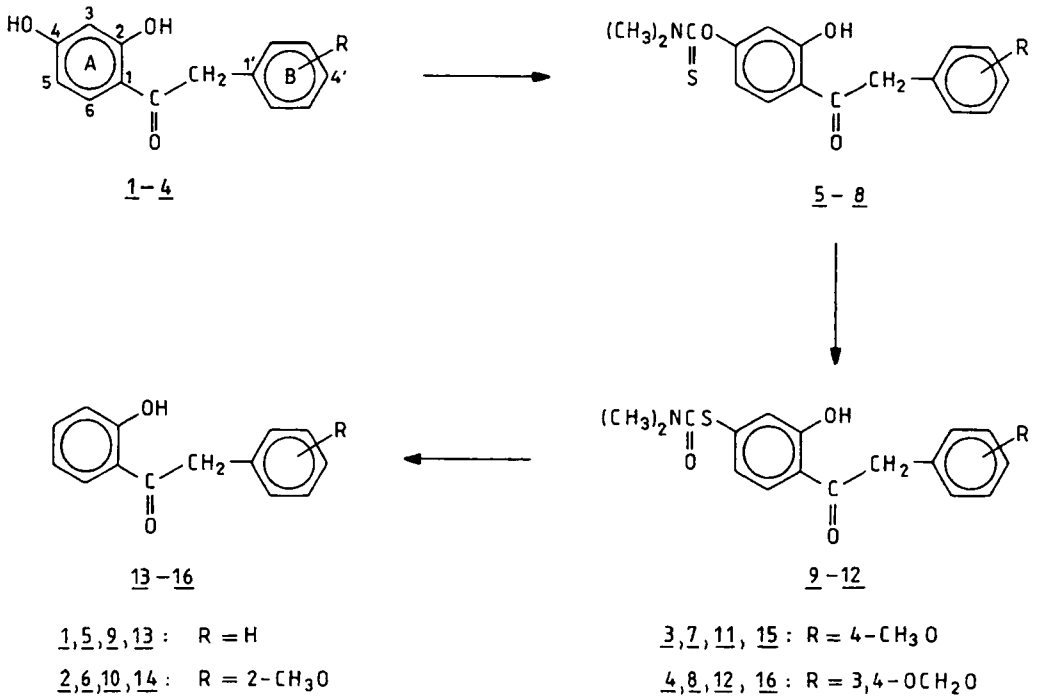
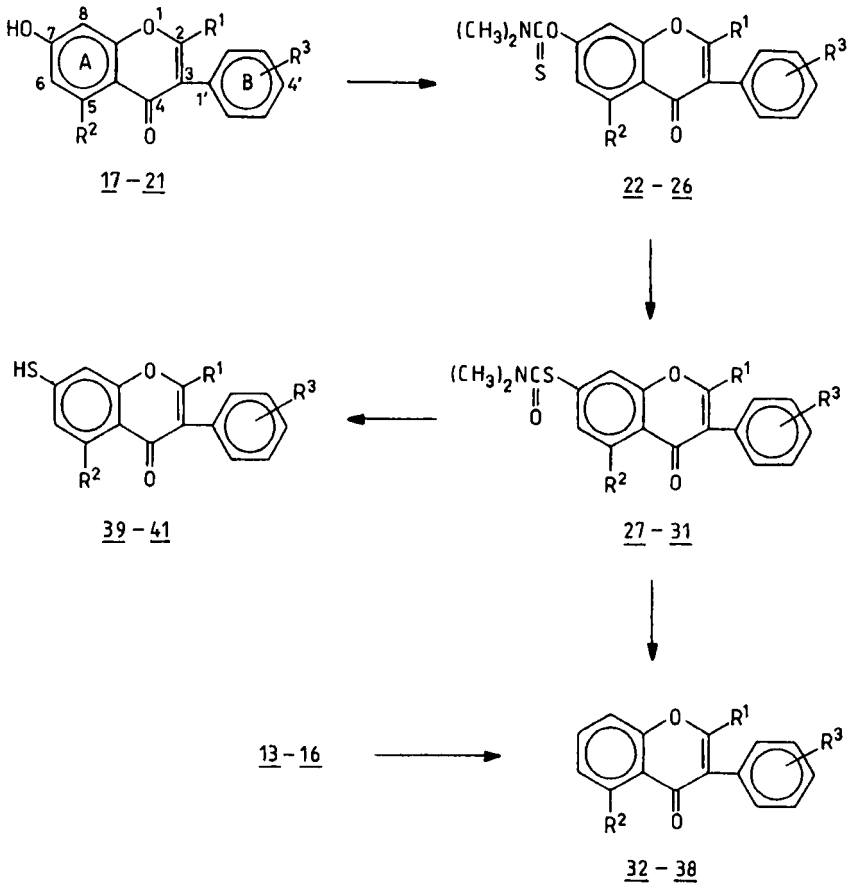
Synthesis of such isoflavones has hitherto been performed mainly by the conversion of 2'-benzyloxychalcone epoxides into isoflavones[1,2] and by the oxidative rearrangement of 2'-hydroxychalcones with thallium(III) nitrate[3] invented by McKillop et al.[4-6] Since the applicability of these methods depends on the substituents of the above-mentioned chalcone derivatives they can, therefore, be used only in special cases. Usual methods, viz. the ring closure of the 2-hydroxydeoxybenzoins could not be used since, except for the parent 2-hydroxydeoxybenzoin[7], 2-hydroxydeoxybenzoins substituted only in their ring B cannot be synthesized by the known procedures. In our present paper we report on the application of the Newman-Kwart rearrangement[8-13] followed by treatment with Raney nickel for selective dehydroxylation of 2,4-dihydroxydeoxybenzoins and 7-hydroxyisoflavone derivatives to make possible the preparation of isoflavones with unsubstituted ring A.

2,4-Dihydroxydeoxybenzoins (1 - 4) were allowed to react with dimethylthiocarbamoyl chloride to afford O-aryl dimethylthiocarbamates 5 - 8 which gave then S-aryl dimethylthiocarbamates 9 - 12 as products of the Newman-Kwart rearrangement. Compounds 9 - 12 were treated with Raney nickel in ethanolic solution to obtain 2-hydroxydeoxybenzoins 13 - 16. This procedure seems to be a convenient method for the selective de-





17, 22, 27, 32 : $R^1 = R^2 = R^3 = H$

— — — 33 : $R^1 = R^2 = H$, $R^3 = 2\text{-}CH_3O$

— — — 34 : $R^1 = R^2 = H$, $R^3 = 4\text{-}CH_3O$

18, 23, 28, 35 : $R^1 = R^2 = H$, $R^3 = 3,4\text{-}OCH_2O$

19, 24, 29, 36, 39 : $R^1 = CH_3$, $R^2 = R^3 = H$

20, 25, 30, 37, 40 : $R^1 = CH_3$, $R^2 = OH$, $R^3 = H$

21, 26, 31, 38, 41 : $R^1 = C_6H_5$, $R^2 = R^3 = H$

hydroxylation of the 2,4-dihydroxydeoxybenzoins affording 2-hydroxydeoxybenzoins as convenient intermediates for the synthesis of isoflavones with unsubstituted ring A. Indeed, substances 13 - 16 have easily been converted (method a) into isoflavones 32 - 35 by the utilization of the method of Karmarker.[14]

7-Hydroxyisoflavones 17 - 21 have also been allowed to react with dimethylthiocarbamoyl chloride to yield O-aryl dimethylthiocarbamates 22 - 26 which were then rearranged into S-aryl dimethylthiocarbamates 27 - 31. Compounds 27 - 31 afforded isoflavones 32 and 35 - 38 on treatment with Raney nickel. This reaction series proved to be an efficient procedure for the dehydroxylation of variously substituted 7-hydroxyisoflavones (17 - 21). In the case of the 5,7-dihydroxy-2-methylisoflavone (20) the regioselectivity of the acylation made possible the preparation of the 5-hydroxy-2-methylisoflavone (37). It is worth mentioning that no procedure has hitherto been developed for the preparation of 5-hydroxyisoflavones. Therefore, the selective dehydroxylation of e.g. 5,7-dihydroxyisoflavones seems to be an advantageous method for the synthesis of 5-hydroxyisoflavones.

Alkaline hydrolysis of compounds 27 - 31 has also been performed and 7-mercaptoisoflavones 39 - 41 have been prepared in this way. 7-Mercaptoisoflavones formed

Table 1

Physical constants of compounds prepared

Compound	M.p. °C	Yield %	Overall formula
5	94 - 95	95	$C_{17}H_{17}NO_3S$
6	168 - 169	91	$C_{18}H_{19}NO_4S$
7	114 - 115	96	$C_{18}H_{19}NO_4S$
8	168 - 169	92	$C_{18}H_{17}NO_5S$
9	100 - 101	87	$C_{17}H_{17}NO_3S$
10	107 - 108	89	$C_{18}H_{19}NO_4S$
11	130 - 131	92	$C_{18}H_{19}NO_4S$
12	160 - 161	91	$C_{18}H_{17}NO_5S$
13	60 - 61[b]	67	$C_{14}H_{12}O_2$
14	59 - 60	71	$C_{15}H_{14}O_3$
15	85 - 86	73	$C_{15}H_{14}O_3$
16	62 - 63	71	$C_{15}H_{12}O_4$
22	195 - 196	85	$C_{18}H_{15}NO_3S$
23	229 - 230	93	$C_{19}H_{15}NO_5S$
24	207 - 208	96	$C_{19}H_{17}NO_3S$
25	208 - 209	90	$C_{19}H_{17}NO_4S$
26	215 - 216	96	$C_{24}H_{19}NO_3S$
27	218 - 219	85	$C_{18}H_{15}NO_3S$
28	240 - 241	90	$C_{19}H_{15}NO_5S$
29	159 - 160	92	$C_{19}H_{17}NO_3S$
30	171 - 172	91	$C_{19}H_{17}NO_4S$
31	208 - 209	82	$C_{24}H_{19}NO_3S$
32	136 - 137[a,c]	91	$C_{15}H_{10}O_2$
33	187 - 188[a,d]	81	$C_{16}H_{12}O_3$
34	140 - 141[a,e]	82	$C_{16}H_{12}O_3$
35	157 - 158[a,f]	81	$C_{16}H_{10}O_4$
36	135 - 136[g]	86	$C_{16}H_{12}O_2$
37	86 - 87	85	$C_{16}H_{12}O_3$

Table 1 continued

Compound	M.p. °C	Yield %	Overall formula
38	143 - 144[h]	93	$C_{21}H_{14}O_2$
39	145 - 146	90	$C_{16}H_{12}O_2S$
40	115 - 116	75	$C_{16}H_{12}O_3S$
41	186 - 187	74	$C_{21}H_{14}O_2S$

[a]Yield refers to method a. Lit. m.p. [b]60 °C[7], [c]136 °C[3], [d]187 - 188 °C[3], [e]140 - 141 °C[3], [f]158 - 159 °C[3], [g]140 °C[7], [h]152 °C[7].

probably from substances 27 and 28 were unstable and could not be isolated and characterized. Our present results reveal that the preparation and chemical transformations of the dimethylthiocarbamate derivatives of the hydroxyisoflavones is a convenient method for the replacement of the hydroxy group by mercapto group as well. To our knowledge, mercaptoisoflavones have not yet been synthesized.

Structure of compounds prepared (5 - 41) has been elucidated by ^{1}H-NMR and mass spectroscopy and the relevant data are summarized in Tables 2 and 3.

Experimental

^{1}H-NMR spectra were recorded on Bruker WP 200 SY and Varian Gemini-200 spectrometers at 200 MHz in $CDCl_3$

Table 2

^{1}H-NMR spectroscopic data of compounds prepared

Compound	δ(ppm)
5	3.32(s, 3H), 3.45(s, 3H), 4.28(s, 2H), 6.68 (dd, 1H, J_1=8.5 Hz, J_2=2.0 Hz), 7.20 - 7.41 (m, 6H), 7.90(d, 1H, J=8.5 Hz), 12.41(s, OH)
6	3.34(s, 3H), 3.44(s, 3H), 3.80(s, 3H), 6.68 (m, 2H), 6.93(m, 2H), 7.23(m, 2H), 7.98(dd, 1H, J_1=9.0 Hz, J_2=2.5 Hz), 12.43(s, OH)
7	3.34(s, 3H), 3.44(s, 3H), 3.81(s, 3H), 4.13(s, 2H), 6.64(m, 2H), 6.89(m, 2H), 7.19(m, 2H), 7.90(dd, 1H, J_1=8.5 Hz, J_2=2.5 Hz), 12.44(s, OH)
8	3.34(s, 3H), 3.44(s, 3H), 4.20(s, 2H), 5.96(s, 2H), 6.71(m, 5H), 7.88(dd, 1H, J_1=8.5 Hz, J_2= =2.0 Hz), 12.40(s, OH)
9	3.08(s, 6H), 4.29(s, 2H), 7.08(dd, 1H, J_1=8.5 Hz, J_2=2.0 Hz), 7.16(d, 1H, J=2.0 Hz), 7.20 - 7.48(m, 5H), 7.85(d, 1H, J=8.5 Hz), 12.20(s, OH)
10	3.06(s, 6H), 3.80(s, 3H), 4.29(s, 2H), 6.86 - 7.35(m, 6H), 7.91(d, 1H, J=9.0 Hz), 12.20(s, OH)
11	3.06(s, 6H), 3.80(s, 3H), 4.22(s, 2H), 6.89(m, 2H), 7.09(m, 2H), 7.19(m, 2H), 7.84(d, 1H, J=8.5 Hz), 12.22(s, OH)
12	3.05(s, 6H), 4.20(s, 2H), 5.96(s, 2H), 6.72(m, 3H), 7.06(dd, 1H, J_1=8.5 Hz, J_2=2.0 Hz), 7.15 (d, 1H, J=2.0 Hz), 7.82(d, 1H, J=8.5 Hz), 12.18 (s, OH)
13	4.31(s, 2H), 6.84 - 7.54(m, 8H), 7.88(dd, 1H, J_1=8.5, J_2=2.0 Hz), 12.24(s, OH)
14	3.80(s, 3H), 4.16(s, 2H), 6.86 - 7.54(m, 7H), 7.93(dd, 1H, J_1=9.0 Hz, J_2=2.5 Hz), 12.24(s, OH)

Compound	δ(ppm)
15	3.79(s, 3H), 4.23(s, 2H), 6.86 - 7.50(m, 7H), 7.86(dd, 1H, J_1=8.5 Hz, J_2=2.5 Hz), 12.22(s, OH)
16	4.22(s, 2H), 5.96(s, 2H), 6.64 - 7.52(m, 6H), 7.86(dd, 1H, J_1=8.5 Hz, J_2=2.5 Hz), 12.22(s, OH)
22	3.40(s, 3H), 3.49(s, 3H), 7.10 - 7.62(m, 7H), 8.01(s, 1H), 8.33(d, 1H, J=9.0 Hz)
23	3.40(s, 3H), 3.49(s, 3H), 6.00(s, 2H), 6.80 - 7.29(m, 5H), 7.97(s, 1H), 8.32(d, 1H , J=9.0 Hz)
24	2.31(s, 3H), 3.40(s, 3H), 3.49(s, 3H), 7.05 - 7.50(m, 7H), 8.25(d, 1H, J=8.5 Hz)
25	2.32(s, 3H), 3.37(s, 3H), 3.48(s, 3H), 6.53(d, 1H, J=2.0 Hz), 6.71(d, 1H, J=2.0 Hz), 7.20 - 7.52(m, 5H), 12.83(s, OH)
26	3.40(s, 3H), 3.49(s, 3H), 7.11 - 7.43(m, 12H), 8.32(d, 1H, J=8.5 Hz)
27	3.12(s, 6H), 7.33 - 7.76(m, 7H), 8.02(s, 1H), 8.30(d, 1H, J=9.0 Hz)
28	3.11(s, 6H), 6.00(s, 2H), 6.87 - 7.70(m, 5H), 7.97(s, 1H), 8.28(d, 1H, J=8.5 Hz)
29	2.31(s, 3H), 3.11(s, 6H), 7.21 - 7.51(m, 6H), 7.68(d, 1H, J=1.5 Hz), 8.20(d, 1H, J=8.5 Hz)
30	2.31(s, 3H), 3.09(s, 6H), 6.92(d, 1H, J=2.0 Hz), 7.15(d, 1H, J=2.0 Hz), 7.21 - 7.51(m, 5H), 12.64(s, OH)
31	3.08(s, 3H), 3.12(s, 3H), 7.15 - 7.44(m, 10H), 7.52(dd, 1H, J_1=8.5 Hz, J_2=1.5 Hz), 7.78(d, 1H, J=1.5 Hz), 8.27(d, 1H, J=8.5 Hz)
32	7.23 - 7.75(m, 8H), 8.02(s, 1H), 8.32(dd, 1H, J_1=9.0 Hz, J_2=2.0 Hz)
33	3.80(s, 3H), 7.02 - 7.68(m, 7H), 8.00(s, 1H), 8.30(dd, 1H, J_1=9.0 Hz, J_2=2.5 Hz)

continued

Table 2 continued

Compound	δ(ppm)
34	3.84(s, 3H), 6.99 - 7.68(m, 7H), 8.01(s, 1H), 8.32(dd, 1H, J_1=8.5 Hz, J_2=2.5 Hz)
35	6.01(s, 2H), 6.88 - 7.68(m, 6H), 8.00(s, 1H), 8.32(dd, 1H, J_1=8.5 Hz, J_2=2.0 Hz)
36	2.32(s, 3H), 7.17 - 7.66(m, 8H), 8.23(dd, 1H, J_1=8.0 Hz, J_2=1.5 Hz)
37	2.17(s, 3H), 6.37 - 6.82(m, 8H), 12.35(s, OH)
38	7.07 - 7.70(m, 13H), 8.30(dd, 1H, J_1=8.0 Hz, J_2=1.5 Hz)
39	2.29(s, 3H), 3.72(s, SH), 7.12 - 7.51(m, 7H), 8.05(d, 1H, J=8.5 Hz)
40	2.28(s, 3H), 3.68(s, SH), 6.63 - 7.53(m, 7H), 12.74(s, OH)
41	3.76(s, SH), 7.16 - 7.45(m, 12H), 8.15(d, 1H, J=15.1)

(internal standard TMS, δ = 0.0 ppm) at room temperature. Mass spectra were measured with a VG apparatus. Starting materials 1 - 4 and 17 - 21 were synthesized according to known procedures.[14-18]

Synthesis of O-Aryl dimethylthiocarbamates 5 - 8 and 22 - 26

A mixture of compounds 1 - 4 and 17 - 21 (10 mmol), dimethylthiocarbamoyl chloride (20 mmol), 1,4-diazabicyclo[2,2,2]octane (20 mmol), and anhydrous

N,N-dimethylformamide (30 ml) was stirred at room temperature for 2 h, then poured into 5% hydrochloric acid (300 ml). The precipitate was filtered off, washed free of acid, and crystallized from methanol to afford compounds 5 - 8 and 22 - 26.

Preparation of S-Aryl dimethylthiocarbamates 9 - 12 and 27 - 31

Compounds 5 - 8 and 22 - 26 (10 mmol) were dissolved in N,N-dimethylaniline (30 ml) and refluxed for 1 h, then poured into 10% hydrochloric acid (300 ml). The precipitate was filtered off, washed free of acid and crystallized from methanol to obtain substances 9 - 12 and 27 - 31.

2-Hydroxydeoxybenzoins 13 - 16

A mixture of substances 9 - 12 (5.0 mmol), Raney nickel (10.0 g), and ethanol (100 ml) was stirred at room temperature for 1 h, the solid material filtered off, the solvent evaporated, and the residue purified by column chromatography to yield crystalline products 13 - 16.

General Procedures for the Preparation of Isoflavones 32 - 38

a./ A mixture of 2-hydroxydeoxybenzoins 13 - 16 (0.1 g), anhydrous pyridine (5.0 ml), anhydrous tri-

Table 3

Mass spectroscopic data of compounds prepared

Compound	m/z (% relative intensity)
5	315(M^+, 3), 224(20), 137(16), 88(100), 72(92)
6	345(M^+, 4), 224(35), 137(3), 121(5), 88(100), 72(38)
7	345(M^+, 3), 224(38), 137(10), 121(19), 88(100), 72(48)
8	359(M^+, 6), 224(28), 135(10), 88(100), 72(37)
9	315(M^+, 3), 224(30), 137(14), 91(12), 88(18), 72(100)
10	345(M^+, 8), 224(37), 121(8), 88(24), 72(100), 43(27)
11	345(M^+, 3), 224(43), 138(5), 121(22), 88(42), 72(100), 57(11)
12	359(M^+, 7), 224(39), 135(20), 102(4), 88(42), 72(100), 57(15)
13	212(M^+, 4), 121(100), 92(10), 77(4), 65(25)
14	242(M^+, 13), 228(5), 121(100), 105(10), 91(29), 77(11), 65(21), 51(7)
15	242(M^+, 10), 121(100), 92(5), 77(5), 65(9)
16	256(M^+, 12), 149(6), 135(20), 121(100), 105(5), 93(10), 77(15)
22	325(M^+, 10), 309(5), 237(5), 88(72), 72(100)
23	369(M^+, 18), 88(100), 72(92)
24	339(M^+, 10), 251(5), 109(8), 88(76), 72(100) 57(22)
25	355(M^+, 8), 115(8), 88(100), 72(85), 55(26)
26	401(M^+, 4), 313(2), 88(75), 72(100)
27	325(M^+, 10), 253(5), 72(100)
28	369(M^+, 10), 297(5), 134(18), 106(10)
29	339(M^+, 10), 267(3), 72(100)

Table 3 continued

Compound	m/z (% relative intensity)
30	355(M^+, 4), 72(100)
31	401(M^+, 4), 72(100), 57(19)
32	222(M^+, 75), 221(92), 165(10), 120(100), 104(25), 92(51)
33	252(M^+, 92), 221(100), 181(5), 165(14), 149(22), 131(81), 121(70), 118(10), 100(12), 89(39)
34	252(M^+, 100), 251(46), 237(27), 209(12), 181(8), 152(11), 132(61), 117(24), 89(49), 76(9), 63(31)
35	266(M^+, 55), 265(40), 222(82), 221(100), 165(10), 146(42), 120(70), 92(52)
36	236(M^+, 56), 235(100), 178(8), 149(9), 115(20), 92(13), 76(8), 63(12)
37	252(M^+, 71), 251(100), 137(16), 136(18), 115(25), 108(26), 89(8)
38	298(M^+, 42), 297(100), 263(13), 178(30), 149(18), 82(47)
39	268(M^+, 75), 267(100), 239(5), 178(8), 153(40), 134(9), 115(51), 96(18)
40	284(M^+, 76), 283(100), 168(8), 142(9), 115(30), 85(10), 69(13), 55(16), 42(41)
41	330(M^+, 16), 297(11), 178(47), 152(17), 112(18), 96(14)

ethylorthoformate (5.0 ml), and piperidine (0.5 ml) was refluxed for 8 h, proured onto ice and acidified with hydrochloric acid. The precipitate was filtered off, washed free of acid and crystallized from methanol to afford isoflavones 32 - 35.

b./ Substances 27 - 31 (5.0 mmol) were treated with Raney nickel (10.0 g) as described for compounds 9 - 12 to obtain white crystalline materials 32 and 35 - 38.

7-Mercaptoisoflavones 39 - 41

Compounds 29 - 31 were refluxed in 10% methanolic potassium hydroxyde solution (50 ml) for 30 min, then the solvent evaporated under reduced pressure. The residue was triturated with water (100 ml) and extracted with diethyl ether (100 ml). The aqueous phase was acidified with hydrochloric acid, the precipitate filtered off, washed free of acid, and crystallized from methanol to yield compounds 39 - 41.

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