Synthesis of 3-Iodoflavans and 2H-Flavenes

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A new synthesis of chromenes, some of which are biologically active, has recently been reported. In this synthesis, substituted 2-allylphenols were first cyclized by reaction with N-iodosuccinimide to form 3-iodochromans, and these were then dehydrohalogenated to 2H-chromenes. This reaction was applied to only one 2-cinnamylphenol, viz. 2-cinnamyl-4-methylphenol (1f). With N-iodosuccinimide it gave a 45% yield of 3-iodo-6-methylflavlan (2f) which with alcoholic potassium hydroxide gave (90%) 6-methyl-2H-flavene (3f). Publication of these results prompts this report of a similar synthesis which was developed almost simultaneously in this laboratory to prepare butylated 3-iodoflavans and flavenes related to butyphenoil insect-growth inhibitors and sterolins.

Our reaction sequence is identical to that of Ref. except that the key, initial cyclization of 2-cinnamylphenols was accomplished very simply by reaction with hydrogen peroxide and an atomic equivalent of iodine. This reagent reacts rapidly with mononuclear and dialkyl-2-cinnamylphenols (1) to give substantially higher yields (80–95%) of 3-iodoflavans (2) than was reported in the reaction of 1f with N-iodosuccinimide. The iodoflavans 2 crystallize in an essentially pure form from the alcohol. The reaction mixture, e.g. the reaction of 2,4-di-i-butyl-6-cinnamylphenol (1a) in alcoholic sulfuric acid with iodoine and hydrogen peroxide, leads to the rapid precipitation of 6,8-di-i-butyl-3-iodoflavlan (2a) in almost quantitative yields. The reaction of 2a with methanolic potassium hydroxide gave 6,8-di-i-butyl-2H-flavene (3a), which was hydrogenated to the flavan 4a.

The stereochemistry of the 3-iodoflavans was indicated by their 1H-N.M.R. spectra. The large coupling constant (J = 9.5 Hz) observed for the proton at C-2 in the spectrum of 2a is in accord with a 2,3-trans configuration, based upon the coupling constants reported for trans,trans and cis,cis-3-bromo-4-hydroxy-4-methoxy-6-methylflavlan. The absence of a C-5 substituent in the 3-iodoflavans prepared in this investigation results in non-equivalence of the benzylic geminal protons at C-4 and complicated ABMX spectra for the C-2,3,4 protons.

The 3-iodoflavans are sensitive to light. A specimen of 2f exposed to diffused light in the laboratory for about a year completely decomposed to a brown black powder, which does not migrate on sillicic acid T.L.C. and appears to be polymeric. Although the photochemistry of 3-iodoflavans has not yet been studied, it is possible that the decomposition may involve photo-dehydrohalogenation and subsequent acid-catalyzed polymerization of the resultant flavene.

6,8-Di-i-butyl-3-iodoflavlan (2a); Typical Procedure:
A solution of 2,4-di-i-butyl-6-cinnamylphenol (1a; 33.2 g, 0.1 mol) in 1% ethanolic sulfuric acid (200 ml) is treated with powdered iodine (12.7 g, 0.05 mol) and 30% hydrogen peroxide (10 ml), warmed to 40–50°C, and stirred until all of the iodine has reacted (1 h). Colorless crystals rapidly separate. Water is added and the product is collected and recrystallized from acetone/methanol to give 2a as colorless needles; yield: 44.0 g (96%); m.p. 120–121°C.

C_{35}H_{30}O calc. C 61.61 H 6.52 J 28.30
(44.8) found 61.7 6.51 28.3

6,8-Di-i-butyl-2H-flavene (3a); Typical Procedure:
A suspension of the iodoflavlan 2a (10 g) in 2% methanolic potassium hydroxide (200 ml) is boiled under reflux until a clear solution is obtained (30 min). The solution is then concentrated and cooled. The crystalline product is isolated by suction and recrystallized from acetone/methanol to give 3a as colorless needles; yield: 7.0 g (98%); m.p. 90°C.

C_{35}H_{30}O calc. C 86.20 H 8.81
(32.0) found 86.1 8.74

6,8-Di-i-butylflavlan (4a); Typical Procedure:
The flavene 3a (1.0 g) is hydrogenated in tetrahydrofuran (20 ml) with hydrogen at ~1 atm over 5% palladium-carbon as catalyst. The reaction mixture is filtered and the residue recrystallized from acetone/methanol to give 4a as colorless needles; yield: 0.85 g (85%); m.p. 127°C.

C_{35}H_{30}O calc. C 85.66 H 9.38
(322.5) found 85.5 9.33

6-Butyl-2H-flavene (3b):
A solution of the iodoflavlan 2b (5 g) in tetrahydrofuran (50 ml) is diluted with 2% methanolic potassium hydroxide (100 ml) and boiled under reflux for 1 h. The solution is concentrated and cooled. The crystalline product is isolated by suction and recrystallized from methanol to give 3b as colorless prisms which melt at room temperature; yield: 2.70 g (80%).

1H-N.M.R. (CDCl3): δ = 1.29 (s, 9H); 1.36 (s, 9H); 1.9–2.3 (m, 2H); 2.7–3.5 (m, 2H); 4.98 (dd, 1H, J = 4 Hz, 9 Hz); 6.94 (br s, 1H); 7.19 (br s, 1H); 7.23–7.55 ppm (m, 3H).

6-Butyl-2H-flavlan (4b):
Compounds 3b (1.0 g) is hydrogenated as described above. The product is recrystallized from methanol to give 4b as colorless needles; yield: 0.85 g (85%); m.p. 70°C.

C_{35}H_{30}O calc. C 85.67 H 8.33
(266.4) found 85.8 8.32
Table. 3-Iodoflavans (2) from 2-Cinnamylphenols (1)

<table>
<thead>
<tr>
<th></th>
<th>Yield [%] of 2</th>
<th>m.p. [°C]</th>
<th>Molecular formula</th>
<th>δ [ppm]</th>
</tr>
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<tbody>
<tr>
<td>1a</td>
<td>96</td>
<td>120–121°</td>
<td>C_{13}H_{17}O</td>
<td>7.35 (m, 5 H)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>(392.3)</td>
<td></td>
</tr>
<tr>
<td>1b</td>
<td>79</td>
<td>169–170°</td>
<td>C_{13}H_{17}O</td>
<td>7.35 (m, 5 H)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>(392.3)</td>
<td></td>
</tr>
<tr>
<td>1c</td>
<td>86</td>
<td>104–105°</td>
<td>C_{13}H_{17}O</td>
<td>7.35 (m, 5 H)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(392.3)</td>
<td></td>
</tr>
<tr>
<td>1d</td>
<td>77</td>
<td>112°</td>
<td>C_{13}H_{17}O</td>
<td>7.35 (m, 5 H)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>(392.3)</td>
<td></td>
</tr>
<tr>
<td>1e</td>
<td>87</td>
<td>119°</td>
<td>C_{13}H_{17}O</td>
<td>7.35 (m, 5 H)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(392.3)</td>
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</tr>
<tr>
<td>1f</td>
<td>84</td>
<td>133–134°</td>
<td>C_{13}H_{17}O</td>
<td>7.35 (m, 5 H)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>(392.3)</td>
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</tr>
</tbody>
</table>

* The microanalyses were in satisfactory agreement with the calculated values: C, ±0.1; H, ±0.1; J, ±0.2.

1'H-N.M.R. (CDCl₃); δ: 1.29 (s, 9 H); 1.95–2.29 (m, 2 H); 2.60–3.25 (m, 2 H); 5.04 (d, 1 H, J = 9 Hz); 6.82 (d, 1 H, J = 7.5 Hz); 7.0–7.2 ppm (m, 7 H).

2-Butyl-4-methyl-6-cinnamylphenol (1c):
A solution of 2- butyl-4-methylphenol (164 g) and cinnamyl alcohol (134 g) in formic acid (400 ml) and water (50 ml) is boiled under reflux for 1.5 h and then diluted with water. Distillation of the oily product gives a fraction (b.p. 183–190°C/0.05 torr) which rapidly crystallizes (167 g). The product is recrystallized from methanol and from Skellysolve F to give 1c as colorless prisms; yield: 117 g (42%); m.p. 81°C.

C₈H₇NO calc. C 85.66 H 8.63
(280.4) found 85.6 8.70

1'H-N.M.R. (CDCl₃); δ: 1.40 (s, 9 H); 2.27 (s, 3 H); 3.51 (d, 2 H, J = 6 Hz); 5.00 (s, 1 H); 6.84 (m, 2 H); 6.83 (d, 1 H, J = 2 Hz); 7.01 (d, 1 H, J = 2 Hz); 7.29 ppm (m, 5 H).

3-Cinnamyl-6-sec-butylphenol and 2-Cinnamyl-4-sec-butylflavan (1d):
A solution of 4-sec-butylphenol (150 g) and cinnamyl alcohol (134 g) in 88% formic acid (400 ml) is refluxed for 1 h, and then diluted with water (1000 ml). The resultant oily product is isolated and distilled in methanol. On cooling, colorless crystals separate. These are collected by suction (the filtrate is saved) and recrystallized from acetone/methanol to give 3-cinnamyl-6-sec-butylflavan as colorless needles; yield: 24.3 g (9%); m.p. 123–124°C.

C₁₃H₁₇NO calc. C 87.91 H 7.91
(382.5) found 87.9 7.82

The methanol filtrate from the above reaction is evaporated and distilled to give a fraction, b.p. 195–200°C/0.5 torr, which crystallizes. The product is recrystallized from Skellysolve F to give 2-cinnamyl-4-sec-butylflavan (1d) as colorless needles; yield: 101 g (38%); m.p. 51–52°C.

C₁₃H₁₇NO calc. C 85.67 H 8.33
(266.4) found 85.3 8.35

1'H-N.M.R. (CDCl₃); δ: 0.82 (t, 3 H, J = 7 Hz); 1.21 (d, 3 H, J = 7 Hz); 1.55 (d, 2 H, J = 7 Hz); 2.53 (m, 1 H); 3.55 (d, 2 H, J = 6 Hz); 4.93 (s, 1 H); 6.24–7.40 ppm (m, 10 H).

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