Preparation of Precocene 2 and 3,4-Epoxyprecocene 2
Deuterated Analogues at C-3, C-4 and C-3, C-4

F. Camps,* A. Conchillo, and A. Messeguer
Instituto de Química Bio-Orgánica (C.S.I.C.), J. Girona Salgado, 18—26, 08034 Barcelona, Spain

Preparation of Precocene 2 and 3,4-Epoxyprecocene 2 Deuterated Analogues

A convenient route for the preparation of title compounds from benzopyran-4-one (1) and its corresponding 3,4-H₂ deuterated analogue (2) is reported. Treatment of 1 or 2 with lithium aluminum deuteride followed by dehydration afforded, respectively, 4⁻H₂ precocene (3e) or 3,4-H₂ precocene (3b). Likewise, reduction of 2 with lithium aluminum hydride and subsequent dehydration led to the formation of 3⁻H₂ precocene (3d). Finally, the corresponding 3,4-epoxy derivatives of all these compounds were prepared in good yields by conventional procedures.

Precocene 2 (3a) is a naturally occurring compound which has been reported to induce strong antihormonal activity in sensitive insects by a selective destruction of the corpora allata, the endocrine glands which secrete juvenile hormone [1]. Since the discovery of this type of allatocidins, several analogues have been synthesized by us and other groups trying to optimize the activity of the natural compounds for potential application of these compounds in biorational insect control strategies [2].

Mode of action and metabolism studies [3] have provided strong evidence that precocenes undergo an oxidative bioactivation within the corpora allata to a highly reactive 3,4-epoxy intermediate (4a). This compound would cause the necrosis of the glands by alkylation of their cellular macromolecules with the ensuing suppression of juvenile hormone biosynthesis.

Consequently, increasing interest on these chemical and biochemical studies has required the availability of straightforward procedures for isotopic labelling of precocenes and its corresponding 3,4-epoxides at definite positions. In this context, several preparations of tritiated precocenes have been described, which include label incorporation at C-4, C-5, methyl and methoxy groups [4]. However, to our knowledge, there is no previous report in the literature on the synthesis of precocenes or its corresponding 3,4-epoxides with specific deuterium monolabelling at C-3 or C-4 and dilabelling at C-3 and C-4. In the present communication, we report an efficient procedure for preparation of these deuterated analogues of precocene 2 and its 3,4-epoxide.

Synthetic pathways assayed for the preparation of title compounds are depicted in the Scheme. Initially, the benzopyran-4-one (1) [5] was treated with 2N deuterated sodium hydroxide under different reaction conditions but incorporation of deuterium did not exceed 20% of the theoretical amount. Conversely, when the method reported by Oae et al. [6], which consists in the treatment of acetophenone derivatives with deuterium oxide and triethylamine in dioxane was assayed with 1, yields of bis deuterated benzopyran-4-one (2) higher than 95% (NMR) were attained after three successive treatments.

Results on the conversion of ketones 1 and 2 into the different deuterated precocenic derivatives and further obtention of their corresponding, 3,4-epoxides are shown in the Table. Accordingly, selective incorporation of deuterium at C-4 was achieved by reduction of the appropriate ketone with lithium aluminum hydride, whereas reduction of ketone 2 with lithium aluminum hydride led to the series of

* Reprint requests to Prof. Dr. F. Camps.
Verlag der Zeitschrift für Naturforschung, D-7400 Tübingen

Diego Camps
Instituto de Química Bio-Orgánica (C.S.I.C.), J. Girona Salgado, 18—26, 08034 Barcelona, Spain

Z. Naturforsch. 40b, 556—558 (1985); received November 23, 1984

Precocene Analogues, Deuteration

A convenient route for the preparation of title compounds from benzopyran-4-one (1) and its corresponding 3,4-H₂ deuterated analogue (2) is reported. Treatment of 1 or 2 with lithium aluminum deuteride followed by dehydration afforded, respectively, 4⁻H₂ precocene (3e) or 3,4-H₂ precocene (3b). Likewise, reduction of 2 with lithium aluminum hydride and subsequent dehydration led to the formation of 3⁻H₂ precocene (3d). Finally, the corresponding 3,4-epoxy derivatives of all these compounds were prepared in good yields by conventional procedures.

Precocene 2 (3a) is a naturally occurring compound which has been reported to induce strong antihormonal activity in sensitive insects by a selective destruction of the corpora allata, the endocrine glands which secrete juvenile hormone [1]. Since the discovery of this type of allatocidins, several analogues have been synthesized by us and other groups trying to optimize the activity of the natural compounds for potential application of these compounds in biorational insect control strategies [2].

Mode of action and metabolism studies [3] have provided strong evidence that precocenes undergo an oxidative bioactivation within the corpora allata to a highly reactive 3,4-epoxy intermediate (4a). This compound would cause the necrosis of the glands by alkylation of their cellular macromolecules with the ensuing suppression of juvenile hormone biosynthesis.

Consequently, increasing interest on these chemical and biochemical studies has required the availability of straightforward procedures for isotopic labelling of precocenes and its corresponding 3,4-epoxides at definite positions. In this context, several preparations of tritiated precocenes have been described, which include label incorporation at C-4, C-5, methyl and methoxy groups [4]. However, to our knowledge, there is no previous report in the literature on the synthesis of precocenes or its corresponding 3,4-epoxides with specific deuterium monolabelling at C-3 or C-4 and dilabelling at C-3 and C-4. In the present communication, we report an efficient procedure for preparation of these deuterated analogues of precocene 2 and its 3,4-epoxide.

Synthetic pathways assayed for the preparation of title compounds are depicted in the Scheme. Initially, the benzopyran-4-one (1) [5] was treated with 2N deuterated sodium hydroxide under different reaction conditions but incorporation of deuterium did not exceed 20% of the theoretical amount. Conversely, when the method reported by Oae et al. [6], which consists in the treatment of acetophenone derivatives with deuterium oxide and triethylamine in dioxane was assayed with 1, yields of bis deuterated benzopyran-4-one (2) higher than 95% (NMR) were attained after three successive treatments.

Results on the conversion of ketones 1 and 2 into the different deuterated precocenic derivatives and further obtention of their corresponding, 3,4-epoxides are shown in the Table. Accordingly, selective incorporation of deuterium at C-4 was achieved by reduction of the appropriate ketone with lithium aluminum hydride, whereas reduction of ketone 2 with lithium aluminum hydride led to the series of

* Reprint requests to Prof. Dr. F. Camps.
Verlag der Zeitschrift für Naturforschung, D-7400 Tübingen

Z. Naturforsch. 40b, 556—558 (1985); received November 23, 1984

Precocene Analogues, Deuteration

A convenient route for the preparation of title compounds from benzopyran-4-one (1) and its corresponding 3,4-H₂ deuterated analogue (2) is reported. Treatment of 1 or 2 with lithium aluminum deuteride followed by dehydration afforded, respectively, 4⁻H₂ precocene (3e) or 3,4-H₂ precocene (3b). Likewise, reduction of 2 with lithium aluminum hydride and subsequent dehydration led to the formation of 3⁻H₂ precocene (3d). Finally, the corresponding 3,4-epoxy derivatives of all these compounds were prepared in good yields by conventional procedures.

Precocene 2 (3a) is a naturally occurring compound which has been reported to induce strong antihormonal activity in sensitive insects by a selective destruction of the corpora allata, the endocrine glands which secrete juvenile hormone [1]. Since the discovery of this type of allatocidins, several analogues have been synthesized by us and other groups trying to optimize the activity of the natural compounds for potential application of these compounds in biorational insect control strategies [2].

Mode of action and metabolism studies [3] have provided strong evidence that precocenes undergo an oxidative bioactivation within the corpora allata to a highly reactive 3,4-epoxy intermediate (4a). This compound would cause the necrosis of the glands by alkylation of their cellular macromolecules with the ensuing suppression of juvenile hormone biosynthesis.

Consequently, increasing interest on these chemical and biochemical studies has required the availability of straightforward procedures for isotopic labelling of precocenes and its corresponding 3,4-epoxides at definite positions. In this context, several preparations of tritiated precocenes have been described, which include label incorporation at C-4, C-5, methyl and methoxy groups [4]. However, to our knowledge, there is no previous report in the literature on the synthesis of precocenes or its corresponding 3,4-epoxides with specific deuterium monolabelling at C-3 or C-4 and dilabelling at C-3 and C-4. In the present communication, we report an efficient procedure for preparation of these deuterated analogues of precocene 2 and its 3,4-epoxide.

Synthetic pathways assayed for the preparation of title compounds are depicted in the Scheme. Initially, the benzopyran-4-one (1) [5] was treated with 2N deuterated sodium hydroxide under different reaction conditions but incorporation of deuterium did not exceed 20% of the theoretical amount. Conversely, when the method reported by Oae et al. [6], which consists in the treatment of acetophenone derivatives with deuterium oxide and triethylamine in dioxane was assayed with 1, yields of bis deuterated benzopyran-4-one (2) higher than 95% (NMR) were attained after three successive treatments.

Results on the conversion of ketones 1 and 2 into the different deuterated precocenic derivatives and further obtention of their corresponding, 3,4-epoxides are shown in the Table. Accordingly, selective incorporation of deuterium at C-4 was achieved by reduction of the appropriate ketone with lithium aluminum hydride, whereas reduction of ketone 2 with lithium aluminum hydride led to the series of
Table. Preparation of deuterated analogues of Precocene 2 (3a) and its corresponding 3,4-epoxy derivatives at C-3, C-4 and C-3,C-4.

<table>
<thead>
<tr>
<th>Start. comp.</th>
<th>Reducing agent</th>
<th>Precocene (yield, %)</th>
<th>3,4-Epoxyprecocene (yield, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AlLiD₄</td>
<td>3c (89)</td>
<td>4c (&gt;90)</td>
</tr>
<tr>
<td>2</td>
<td>AlLiH₄</td>
<td>3d (81)</td>
<td>4d (&gt;90)</td>
</tr>
<tr>
<td>2</td>
<td>AlLiD₄</td>
<td>3b (83)</td>
<td>4b (&gt;90)</td>
</tr>
</tbody>
</table>

* Due to the instability of these compounds, they were not isolated and yields were estimated from ¹H NMR spectra of the crude reaction mixture using 1,1,2,2-tetrachloroethane as internal standard.

Compounds which only have the label at C-3. All compounds were characterized by analytical and spectroscopic means and by comparison with the corresponding non deuterated analogues.

In conclusion, the results herein described permit a convenient preparation of deuterium labelled precocenes and 3,4-epoxyprecocenes at C-3 and C-4 where reactions involved are clean and take place with good yields. These advantages counterbalance the loss of one deuterium atom per molecule inherent to the reduction and further dehydration processes when bis deuterated ketone 2 is used.

Finally, availability of the title labelled compounds has been a valuable tool for the elucidation of di-meric structures encountered in a current study on the reactivity of 3,4-epoxy precocenes [7].

**Experimental**

Melting points were determined on a Kofler apparatus and are uncorrected. Boiling points are referred to bulb-to-bulb distillation. ¹H NMR spectra were registered on a Bruker WP 80 SY spectrometer operating at 80.13 MHz. Samples were observed in deuteriochloroform solutions at normal temperature, the solvent providing the lock signal. All operating at 80.13 MHz. Samples were observed in deuteriochloroform solutions at normal temperature, the solvent providing the lock signal. All chemical shifts are given in ppm downfield from internal tetramethylsilane. GC/MS determinations were performed with a 5995 B Hewlett-Packard apparatus using an OV-101 capillary column.

3,3,3²H₂-2,3-Dihydro-6,7-dimethoxy-2,2-dimethyl-4H-1-benzopyran-4-one (2)

Following the procedure described by Oae et al. [6], triethylamine (0.42 g, 4.6 mmol) and deuterium oxide (0.42 g, 23.3 mmol) were added to a solution of benzopyran-4-one (1) [5] (0.42 g, 1.8 mmol) in dioxane (12.5 ml) and the mixture was stirred for 24 h at 100 °C. After cooling, the crude was concentrated under vacuum and the residue obtained after complete solvents removal was subjected to the same treatment as above. This process was repeated three times to afford a final residue (0.42 g), which contained the bis deuterated ketone 2 with a deuterium incorporation higher than 95% according to ¹H NMR.

2: m.p. 106–107 °C; ¹H NMR (CDCl₃): 1.46 (s, 6H, CH₂), 3.87 (s, 3H, CH₂O), 3.89 (s, 3H, CH₂O), 6.40 (s, 1H, ArH) and 7.27 (s, 1H, ArH) ppm; mass spectrum, m/e (relative intensity): 238 (M⁺, 29), 181 (100).

3,4-²H₂-6,7-Dimethoxy-2,2-dimethyl-2H-1-benzopyran (3b)

To a solution of bis deuterated benzopyran-4-one (2) (0.080 g, 0.34 mmol) in diethyl ether (5 ml), an excess of lithium aluminum deuteride (0.021 g, 0.5 mmol) was added and the mixture was stirred for 1 h at room temperature. After the careful addition of water, inorganic salts were filtered off and the organic solution was vigorously stirred with 6 N hydrochloric acid for 1 h at room temperature. The aqueous fraction was extracted with diethyl ether (2 x 25 ml) and the combined organic fractions were washed with sodium bicarbonate solution, brine and dried over magnesium sulfate. The residue obtained after solvent removal was distilled bulb-to-bulb to afford 0.062 g (83% yield) of a pale yellow oil identified as 3b.

3b: b.p. 125–130 °C (0.3 Torr); ¹H NMR (CDCl₃): 1.41 (s, 6H, CH₂), 3.81 (s, 3H, CH₂O), 3.83 (s, 3H, CH₂O), 6.41 (s, 1H, ArH) and 6.53 (s, 1H, ArH) ppm; mass spectrum, m/e (relative intensity): 222 (M⁺, 14), 207 (100).

4-²H₂-6,7-Dimethoxy-2,2-dimethyl-4H-1-benzopyran (3c)

Following the same procedure above described, benzopyran-4-one (1) (0.056 g, 2.4 mmol) was treated with lithium aluminum deuteride (0.15 g, 3.6 mmol). Bulb-to-bulb distillation of the residue obtained after acid treatment afforded 3c (0.047 g, 89% yield) as a pale yellow oil.

3c: b.p. 125–130 °C (0.3 Torr); ¹H NMR (CDCl₃): 1.41 (s, 6H, CH₂), 3.81 (s, 3H, CH₂O), 3.83 (s, 3H, CH₂O), 5.47 (s, 1H, H-3), 6.41 (s, 1H, ArH) and 6.53 (s, 1H, ArH) ppm; mass spectrum, m/e (relative intensity): 221 (M⁺, 17), 206 (100).

3,3²H₂-6,7-Dimethoxy-2,2-dimethyl-2H-1-benzopyran (3d)

Following the same procedure above described, benzopyran-4-one (2) (0.080 g, 0.34 mmol) was treated...
ated with lithium aluminum hydride (0.019 g, 0.50 mmol). Bulb-to-bulb distillation of the residue obtained after acid treatment afforded 4c (0.060 g, 81% yield) as a pale yellow oil.

3d: b.p. 125–130 °C (0.3 Torr); \(^1\)H NMR (CDCl\(_3\)): 1.41 (s, 6H, CH\(_3\)), 3.81 (s, 3H, CH\(_3\)O), 3.83 (s, 3H, CH\(_3\)O), 6.23 (s, 1H, \(\text{H-4}\)), 6.41 (s, 1H, ArH) and 6.53 (s, 1H, ArH) ppm; mass spectrum, \(m/e\) (relative intensity): 221 (M\(^+\), 16), 206 (100).

Deuterated 3,4-dihydro-3,4-epoxy-6,7-dimethoxy-2,2-dimethyl-2\(^H\)-1-benzopyrans (4b–d)

**General Procedure** [8]

A solution of N-bromosuccinimide (NBS) in tetrahydrofuran was added dropwise to a solution of the corresponding 2\(^H\)-1-benzopyran (3b–d) in tetrahydrofuran-water (1:1) maintained at 0–5 °C (NBS: 3b–d/1.1:1 molar ratio). After reaction was completed (15 min, TLC monitoring), tetrahydrofuran was removed under vacuum and the aqueous residue was extracted with diethyl ether. The combined organic fractions were washed with 0.5 N hydrochloric acid, brine and dried over magnesium sulfate. The residue obtained after solvent removal, which contained the crude bromohydrin, was solved in dry tetrahydrofuran and the solution was added, under nitrogen, to a dispersion of sodium hydride in the same solvent (sodium hydride: substrate/1.5:1 molar ratio). After addition, the mixture was vigorously stirred for 1 h at 50 °C and then 20 h at room temperature. The crude reaction mixture was filtered off to eliminate inorganic salts and the filtrate, which contained the crude 3,4-epoxide, was stored at 4 °C. Under these conditions, compounds 4b–d remained indefinitely stable. Conversion yields were estimated by \(^1\)H NMR using 1,1,2,2-tetra-chloroethane as internal standard and in all cases values over 90% were obtained.

4b: \(^1\)H NMR (CDCl\(_3\)): 1.24 (s, 3H, CH\(_3\)), 1.56 (s, 3H, CH\(_3\)), 3.81 (s, 3H, CH\(_3\)O), 3.85 (s, 3H, CH\(_3\)O), 6.41 (s, 1H, ArH) and 6.84 (s, 1H, ArH) ppm; mass spectrum, \(m/e\) (relative intensity): 238 (M\(^+\), 32), 237 (56), 236 (25), 169 (50), 168 (100), 167 (63).

4c: \(^1\)H NMR (CDCl\(_3\)): 1.25 (s, 3H, CH\(_3\)), 1.56 (s, 3H, CH\(_3\)), 3.44 (s, 1H, \(\text{H-3}\)), 3.82 (s, 3H, CH\(_3\)O), 3.85 (s, 3H, CH\(_3\)O), 6.41 (s, 1H, ArH) and 6.84 (s, 1H, ArH) ppm; mass spectrum, \(m/e\) (relative intensity): 237 (M\(^+\), 59), 236 (36), 194 (100), 193 (64).

4d: \(^1\)H NMR (CDCl\(_3\)): 1.24 (s, 3H, CH\(_3\)), 1.56 (s, 3H, CH\(_3\)), 3.81 (s, 3H, CH\(_3\)O), 3.82 (s, 3H, CH\(_3\)O), 3.85 (s, 3H, CH\(_3\)O), 6.41 (s, 1H, ArH) and 6.83 (s, 1H, ArH) ppm; mass spectrum, \(m/e\) (relative intensity): 237 (M\(^+\), 47), 236 (49), 168 (75), 167 (100).

The authors thank Dr. J. Coll for many helpful discussions. Financial support from Comisión Asesora para la Investigación Científica y Técnica (Grant 1664/82) is gratefully acknowledged.

---