Synthesis of Models of Metabolites: Oxidation of Variously Substituted Chromenes Including Acronycine, by a Porphyrin Catalytic System

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The influence of chemical neighbouring on oxidation of substituted 2,2-dimethylchromenes derivatives **5**-**8** by a biomimetic catalytic system was first studied. It was then applied to acronycine an anti-cancer drug in order to obtain in one single step oxidized products resulting from the reactivity of the 1,2-double bond in the pyranic D-ring. These 2,2-dimethylchromenes constitute the structural moiety responsible for the activity of acronycine. This oxidation showed the sensitivity of the ethylenic bond, leading to the formation of the corresponding epoxides, diols and/or ketoalcohol. In the case of 5-dimethylamino-2,2-dimethylchromene **8**, the double bond was not sensitive to oxidation, but the *N*-methyl groups reacted to lead to the formamide derivative **16** and an imino-alcohol **17**. This methodology applied to acronycine molecule **1**, allowed to obtain in one step, two oxidized compounds, a *trans*-diol **3** and a ketoalcohol **4** under preparative conditions.

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Metabolic studies in living animals can be limited by the toxicity of a drug. Most often, it is not possible to administer an anticancer drug during a long period, and alternative methods are necessary to access models of metabolites. In the particular case of acronycine (Figure 1, compound **1**), a natural alkaloid isolated from *Acronychia baueri* Schott, a supplementary difficulty is caused by its very weak water-solubility, which excludes parenteral formulation of the drug [1]. Thus, only some experiments have been realized *in vivo* [2]. Results of these biotransformations have shown a reactivity of one of the methyl groups linked on the D-ring or an hydroxylation on various positions of the A-ring. Nevertheless, several studies proved that the 1,2-double bond of the pyranic D-ring was the main structural moiety of the molecule responsible for anticancer activity [3-7].

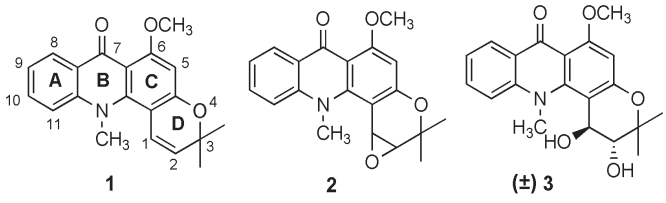
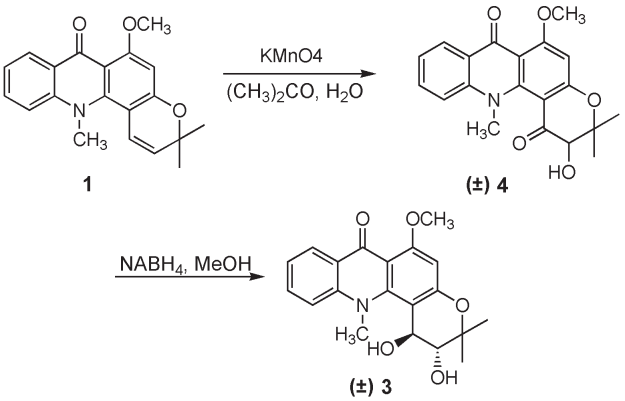


Figure 1. Acronycine and its metabolites.

Recent published results allowed to consider acronycine 1,2-epoxide (Figure 1, compound **2**) as the metabolite which *in vivo* plays a major role in the anti-tumor activity of acronycine [8]. Moreover, hydroxylated acronycine analogs on the double bond have constituted excellent chemical intermediates to access to more cytotoxic derivatives [8,9]. In particular, the *trans*-1,2-dihydroxy-1,2-dihydro-acronycine (Figure 1, compound **3**) isolated from *Sarmelicope glauca* [10] proved to be a suitable candidate for esterification reactions leading to active derivatives.

But, extraction yields of compounds from plants are often weak. Microbiological methods did not allow one to obtain any metabolites resulting from oxidation of the 1,2-double bond [11]. Direct chemical oxidation of acronycine by potassium permanganate [1] allowed for the preparation of the *trans*-diol of acronycine **3**, but in two steps. Direct oxidation led to a ketoalcohol **4**, and had to be followed by reduction of the keto function (Scheme 1) [1].

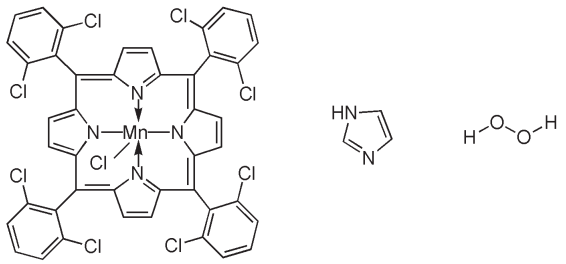
Scheme 1.



Acronycine chemical oxidation by $KMnO_4$.

The original preparative chemical method using the biomimetic catalytic system Mn(TDCPP)Cl [TDCPP stands

for tetrakis-(2,6-dichloro-phenyl)porphyrin]/imidazole/H_2O_2 had recently proved a great efficiency in the synthesis of models of metabolites of bioactive compounds (Figure 2) [12-14]. This approach allowed for example to obtain, in a one-pot synthesis, sufficient amounts of several oxidized products, in the case of octalones precursors of steroids [14].



Mn^{III}(TDCPP)Cl

Figure 2. Mn^{III}(TDCPP)Cl, imidazole, perhydrol.

This novel method could then be applied to acronycine in order to obtain, in one single step, oxidized products resulting from the reactivity of the 1,2-double bond in the pyranic D-ring. Before applying the method to the tetracyclic alkaloid itself, it was necessary to study the influence of chemical neighbouring on the reactivity of this ethylenic bond. Compounds **5**-**8** (Figure 3) constitute models of the essential structural moiety responsible for acronycine activity. Oxidation of these compounds by the biomimetic manganese/porphyrin/imidazole catalytic system, was then studied.

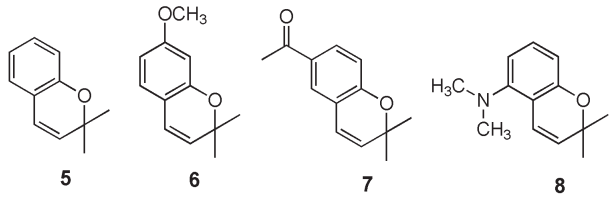
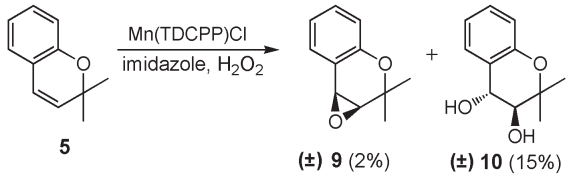


Figure 3. Chromenes **5**-**8**.

Oxidation of 2,2-dimethylchromenes (**5-8**).

Oxidation of these substrates by the catalytic system Mn(TDCPP)Cl/imidazole/H_2O_2 occurred on the 3,4-double bond (equivalent to 1,2-double bond in acronycine) for compounds **5**, **6** and **7**. The sensitivity of this ethylenic bond was slightly modified according to the nature and the position of substituents on the 2,2-dimethylchromene synthon. Compounds **5** and **6** showed a similar reactivity. Unsubstituted dimethylchromene **5** gave mainly a *trans*-diol **10** and an epoxide **9** with very weak yields (Scheme 2). Ths *cis*-epoxide **9** was stable enough to be isolated by column chromatography without any transformation into the corresponding diol.

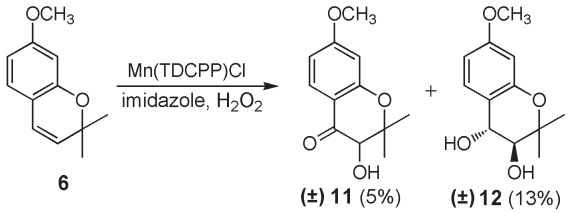
Scheme 2



2,2-Dimethylchromene oxidation.

No formation of epoxide was observed in the case of the 7-methoxy analog **6**, but a keto alcohol **11** was isolated in 5% yield, in addition to the corresponding *trans*-diol **12** (Scheme 3).

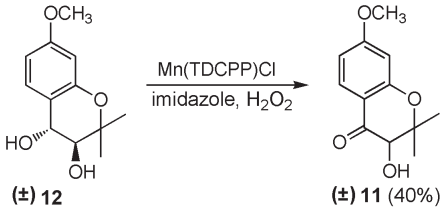
Scheme 3



Scheme 3. 7-Methoxy-2,2-dimethylchromene oxidation.

Hypothesis was made that the ketoalcohol **11** resulted from an oxidation at a higher degree from the corresponding dihydroxy derivative (Scheme 4). In order to prove this hypothesis, the diol **12** was submitted to a second reaction catalyzed by the system Mn(TDCPP)Cl/imidazole/H_2O_2, under the same conditions as the first oxidation. This reaction gave compound **11** in 40% yield. The hydroxy group on C-4 in **12** underwent an additional oxidation leading to a keto group conjugated with the phenyl.

Scheme 4



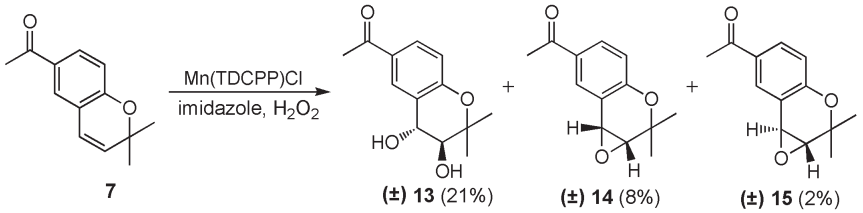
3,4-Dihydroxy-7-methoxy-2,2-dimethylchromane oxidation.

Amongst the four chromenes, the 6-acetyl analog **7** proved to be the most reactive. Its oxidation led to the formation of a *trans*-diol **13** together with two epoxides (*cis*-epoxide **14** and *trans*-epoxide **15**) in 31% total yield (Scheme 5). Even if *cis*-epoxides were more common, the formation of conformationally rigid systems such as *trans*-epoxides had already been described in some cases [15,16]. The epoxides **14** and **15** were characterized by ^{1}H NMR spectroscopy and mass spectrometry. In this experiment, the formation of the *trans*-epoxide **15** was proved by comparison of spectral data to those of the *cis* **14**. The mass spectrum showed a molecular peak at M^{+-} = 218 for both isomers. The original Karplus equation [16,17] is not applicable in the case of rigid compounds. Anyway, in such conformationally restricted systems, a specific Karplus-like relationship exists between the dihedral angle and the corresponding vicinal proton – proton coupling constant [18]. The vicinal coupling constant between H-3 (3.5 ppm) and H-4 (3.9 ppm) is 4.2 Hz for compound **14**, while it is 8.9 Hz for compound **15**. The high coupling constant between H-3 and H-4 is only in agreement with a *trans* stereochemistry. The difference between ^{13}C NMR chemical shifts $\Delta\delta$ for C-3 and C-4 was 11.8 ppm for *cis*-epoxide **14**, and 16.4 ppm for *trans*-epoxide **15**. This observation is in agreement with what was observed for *trans* and *cis*-10-methyldecalin epoxides ($\Delta\delta$ = 16.8 ppm for *trans* and $\Delta\delta$ = 12.1 ppm for *cis*-isomer) [19]. Moreover, the weak yield (2%) obtained for the strained *trans*-epoxide **15** can be explained by its instability during the chromatographic purification process. This low stability was experimentally proved when a pure sample of the *trans*-epoxide **15** was submitted to a second chromatography on silica gel, a ring opening occured and it led to a corresponding diol (in fact, it was the *trans*-diol **13**).

Concerning the *N,N*-dimethyl-2,2-dimethylchromene **8**, the double bond was not sensitive to oxidation, but methyl groups on the nitrogen atom reacted to lead to the formamide derivative **16** and an imino-alcohol **17** resulting from a dealkylation of **16** (Scheme 6). Carbon atoms in α position of amino groups were sensitive to oxidation by this catalytic manganoporphyrin system. This behaviour had already been observed in the case of imidazole oxidation, leading to carbonyl groups [12]. Furthermore, the demethylation of *N,N*-dimethylamides often occured in oxidation processes [20,21].

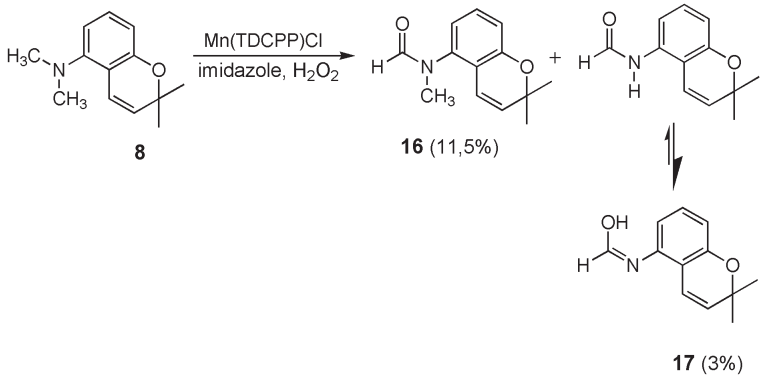
These results showed that the presence of a carbonyl group in position 6 favoured the oxidation of the double bond, while the presence of a nitrogen atom in position 5 lowered the sensitivity of the double bond to oxidation. These two functions being both included in acronycine formula it was interesting to study the relative influence of both these functions on the behaviour of the double bond in this alkaloid.

Scheme 5



6-Acetyl-2,2-dimethylchromane oxidation.

Scheme 6



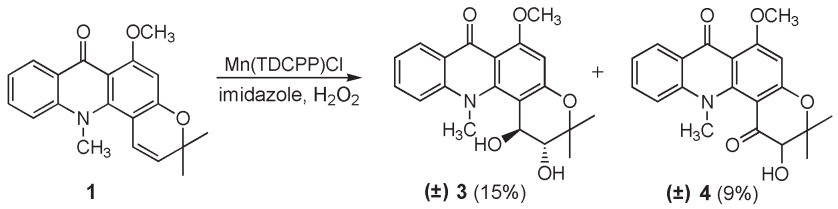
N,N-Dimethyl-2,2-dimethylchromene oxidation.

Oxidation of Acronycine (**1**).

Oxidation of this anticancer agent presented two major interests. The first was to compare the sensitivity of the different positions, which could potentially be oxidized to more functionalized chemical structures. The second advantage of this approach was to prepare models of metabolites from acronycine.

Oxidation of acronycine by hydrogen peroxide catalyzed by Mn(TDCPP)Cl in the presence of imidazole (same conditions as previuos oxidations) led to two oxidized products, the *trans*-diol **3** and the ketoalcohol **4** (Scheme 7). In both cases, the ethylenic bond proved to be the most reactive part of the molecule despite the presence of an aminomethyl group. In opposition to what occured in open systems, the aminomethyl group when it was included in a quinolone ring, was not able to protect the double bond from oxidation. On the other hand, the presence of a carbonyl in position β to the nitrogen atom activated the double bond as it was the case for compound **7**. Oxidation of the ethylenic bond occurred in acronycine as it had already been the case for chromenes **5** – **7**.

Scheme 7



Acronycine oxidation by Mn(TDCPP)Cl.

Nevertheless, no epoxide was isolated, probably due to the very low stability of such a structure included in a bulky system as acronycine.

Direct acronycine oxidation in these two oxidized compounds constituted an interesting result, because the other chemical method, using potassium permanganate had only given the ketoalcohol **4**. The obtention of **3** needing then either another chemical step (reduction) or an extraction from *Sarcomelicope glauca*. Thus, the use of Mn(TDCPP)Cl proved to be an essential tool to obtain in one single step sufficient amounts of oxidized products from acronycine, and it allowed to synthesize major chemical intermediates for the development of the structure-activity relationships in the acronycine series.

EXPERIMENTAL

Melting points were determined on a Kofler hot-plate melting point apparatus and are not corrected. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were taken on a Brüker Avance DPX spectrometer. ^{1}H NMR and ^{13}C NMR spectra were obtained in $CDCl_3$ with tetramethysilane as an internal standard. Mass spectra were obtained on a GC-MS system. An Agilent 6890 gas chromatograph was equipped with a non polar capillary column; the carrier gas was helium. The mass spectrometer (Hewlett Packard 5970 MSD) was operating in electron impact mode (70 eV) and directly interfaced with the gas chromatograph apparatus.

Mn(TDCPP)Cl was prepared according to published procedures [22-25]. The 2,2-dimethylchromenes (**5-7**) and acronycine (**1**) were prepared according to the method previously described [6].

5-Dimethylamino-2,2-dimethylchromene (**8**).

To a solution of 5-amino-2,2-dimethylchromene [6] (1.05 g, 6 mmoles) in dry THF (10 ml) was added sodium hydride (0.72 g, 18 moles, 60% dispersion in oil). The mixture was stirred for thirty minutes, methyl iodide (1.2 ml, 18 mmoles) was added, and the reaction mixture was refluxed for eleven hours, sodium hydride (0.36 g, 9 mmoles) and sodium iodide (0.6 ml, 9 mmoles) were then added. The reaction mixture was refluxed for 48 additional h. The solvent was evaporated under reduced pressure. The residue was dissolved in 15 ml of ammonium chloride, then extracted with 4 x 15 ml of ethyl acetate. The organic layers were collected and dried over sodium sulfate. The solvent was removed *in vacuo*. The crude product was purified *via* chromatography (solid phase: SiO_2, solvent: CH_2Cl_2). Compound **8** was obtained in 95% yield; ir: 3215, 2975 cm^{-1}; ^{1}H nmr: δ 1.22 (s, 6H, 2 x CH_3) ; 2.52 (s, 6H, 2x CH_3), 5.38 (d, 1H, H-3, J = 9.8 Hz), 6.27-6.33 (m, 2H, 6-H and H-8), 6.40 (d, 1H, H-4, J = 9.8 Hz), 6.83 (t, 1H, H-7, J = 8.0 Hz); ^{13}C nmr: δ 27.7 (C_2-*CH$_3$*), 45.0 (*N*-CH_3), 75.1 (C-2), 110.0 (C-8), 110.9 (C-6), 115.0 (C-4a), 120.4 (C-4), 128.5 (C-3), 129.2 (C-7), 151.2 (C-5), 154.4 (C-8a); ms: m/z 203 ($M^{+\bullet}$, 53), 189 (22), 188 (100), 173 (17), 172 (24), 160 (12), 144 (9), 93 (15).

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.86; H, 8.36; N, 6.89. Found: C, 76.58; H, 8.61; N, 7.02.

General Procedure for Oxidation of Acronycine **1** and Substrates **5-8**.

A solution of Mn(TDCPP)Cl (0.25 mmol), imidazole (1 mmole) and substrate (10 mmoles) in 33 ml of dichloromethane/acetonitrile (1/1, v/v) was prepared in a flask. In another flask, imidazole (5 mmoles) was dissolved in 45 ml of acetonitrile, then hydrogen peroxide (35% in water, 5 ml) was added. This mixture was added dropwise (during two hours) at room temperature to the first solution. The mixture was stirred at room temperature for

two more hours. The solvent was then evaporated under reduced pressure, and the residual oil was chromatographed (solid phase: silica gel, solvent: dry acetone) in order to separate the products from the catalyst. A second chromatography (solid phase: silica gel; solvent: see below) was necessary to separate the different oxidized products of the reaction.

Oxidation of acronycine **1**.

The solvent for the second chromatography was cyclohexane/dry acetone (1/1, v/v). Both isolated compounds **3** (yield: 15%) and **4** (yield: 9%) were already known compounds[1,10].

Oxidation of 2,2-Dimethylchromene **5**.

The solvent for the second chromatography was cyclohexane/ethyl acetate (1/2, v/v). Both isolated compounds 3,4-epoxy-2,2-dimethyl-chromane **9** (yield: 2%) and 3,4-dihydroxy-2,2-dimethylchromane **10** (yield: 15%) were already known compounds [26-30].

Oxidation of 7-Methoxy-2,2-dimethylchromene **6**.

The solvent for the second chromatography was cyclohexane/ethyl acetate (1/1, v/v). 3,4-Dihydroxy-7-methoxy-2,2-dimethylchromane **12** (yield: 13%) was a known compound [30-32].

3-Hydroxy-7-méthoxy-2,2-dimethylchroman-4-one (**11**).

This compound was obtained in 5% yield; ir: 3450, 2920, 1660, 1585 cm^{-1}; ^1H nmr: δ 1.18 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 3.72 (d, 1H, OH, J = 2.2 Hz), 3.76 (s, 3H, OCH_3), 4.28 (d, 1H, H-3, J = 2.2 Hz), 6.31 (d, 1H, H-8, J= 2.0 Hz), 6.50 (dd, 1H, H-6, J = 2.0, 9.0 Hz), 7,68 (d, 1H, H-5, J = 9.0 Hz); ^{13}C nmr: δ 19.7 (CH_3), 27.3 (CH_3), 56.3 (OCH_3), 76.2 (C-3), 82.1 (C-2), 101.7 (C-6), 110.3 (C-8), 112.6 (C-4a), 128.8 (C-5), 162.3 (C-8a), 167.3 (C-7), 193.0 (C-4); ms: m/z 222 ($M^{+\bullet}$, 34), 193 (20), 178 (5), 152 (12), 151 (100).

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.89; H, 6.30. Found: C, 64.72; H, 6.69.

Oxidation of 6-Acetyl-2,2-dimethylchromene **7**.

The solvent for the second chromatography was cyclohexane/ethyl acetate (7/3, v/v).

3,4-Dihydroxy-6-acetyl-2,2-dimethylchromane (**13**).

This compound was obtained in 21% yield; mp 129-131°; ir: 3450, 3050, 2980, 1614 cm^{-1}; ^1H nmr: δ 1.17 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 2.40(s, 3H, CH_3CO), 3.51 (d, 1H, H-3, J = 8.9 Hz), 4.50 (d, 1H, H-4, J = 8.9 Hz), 4.60 (s broad, 1H, OH), 5.00 (s broad 1H, OH), 6.65 (d, 1H, H-8, J = 8.7 Hz), 7.63 (d, 1H, H-7, J = 8.7 Hz), 8.00 (s, 1H, H-5); ^{13}C nmr: δ 19.5 (CH_3), 26.9 (CH_3), 27.0 (CH_3CO), 69.2 (C-4), 75.8 (C-3), 80.2 (C-2), 117.2 (C-8), 124.1 (C-4a), 129.3 (C-6), 130.2 (C-7), 130.2 (C-5), 157.2 (C-8a), 198.3 (C=O); ms: m/z 236 ($M^{+\bullet}$, 39), 218 (11), 187 (89), 175 (38), 165 100), 163 (27), 149 (53), 72 (34).

Anal. Calcd. for $C_{13}H_{16}O_4$: C, 66.12; H, 6.77. Found: C, 65.81; H, 6.57.

Cis-3,4-Epoxy-6-acetyl-2,2-dimethylchromane (**14**).

This compound was obtained in 8% yield; mp 119-121°; ir: 3050, 2935, 1385, 1270 cm^{-1}; ^1H nmr: δ 1.22 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 2.50 (s, 3H, CH_3CO), 3.47 (d, 1H, H-3, J = 4.2 Hz), 3.90 (d, 1H, H-4, J = 4.2 Hz), 6.78(d, 1H, H-8, J = 8.3 Hz), 7.89 (d, 1H, H-7, J = 8.3 Hz), 7.94 (s, 1H, H-5); ^{13}C nmr: δ 23.4 (CH_3), 25.9 (CH_3), 26.7 (CH_3CO), 51.0 (C-4), 62.8 (C-3), 74.7 (C-2), 118.4 (C-8), 120.2 (C-4a), 130.0 (C-7), 130.9 (C-6), 131.6 (C-5), 157.4 (C-8a), 196.9 (C=O). ms: m/z 218 ($M^{+\bullet}$, 48), 203 (12), 187 (42), 175 (100), 162 (32), 147 (42).

Anal. Calcd. for $C_{13}H_{14}O_4$: C, 71.58; H, 6.41. Found: C, 71.23; H, 6.18.

Trans-3,4-Epoxy-6-acetyl-2,2-dimethylchromane (**15**).

This compound was obtained in 2% yield; mp 109-111°; ir: 3050, 2935, 1385, 1270 cm^{-1}; ^1H nmr: δ 1.19 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 2.50 (s, 3H, CH_3CO), 3.79 (d, 1H, H-3, J = 8.9 Hz), 4.92 (d, 1H, H-4, J = 8.9 Hz), 6.77 (d, 1H, H-8, J = 8.3 Hz), 7.74 (d, 1H, H-7, J = 8.3 Hz), 8.06 (s, 1H, H-5); ^{13}C nmr: δ 19.2 (CH_{3a}), 27.0 (CH_{3b}), 27.2 (CH_3CO), 60.1 (C-4), 76.5 (C-3), 80.1 (C-2), 117.8 (C-8), 120.9 (C-4a), 130.7 (C-7), 131.0 (C-6), 131.7 (C-5), 156.8 (C-8a), 197.1 (C=O); ms: m/z 218 ($M^{+\bullet}$, 25), 203 (3), 190 (9), 176 (12), 175 (100).

Anal. Calcd. for $C_{13}H_{14}O_3$: C, 71.58; H, 6.41. Found: C,71.10; H, 6.15.

Oxidation of 5-Dimethylamino-2,2-dimethylchromene **8**.

The solvent for the second chromatography was cyclohexane/ethyl acetate (1/1, v/v).

5-*N*-Methylformamido-2,2-dimethylchromene (**16**).

This compound was obtained in 11.5% yield; ir: 3000, 1690, 1620, 1490 cm^{-1}; ^1H nmr: δ 1.38 (s, 6H, 2 x CH_3), 3.15 (s, 3H, *N*-CH_3), 5.64 (d, 1H, H-3, J = 10.0 Hz), 6.21 (d, 1H, H-4, J = 10.0 Hz), 6.61 (d, 1H, H-6, J = 8.0 Hz), 6.73 (d, 1H, H-8, J = 8.0 Hz), 7,05 (t, 1H, H-7, J = 8.0 Hz), 8.08 (s, 1H, CHO); ^{13}C nmr: δ 28.1 (C_2-CH_3), 34.2 (*N*-CH_3), 76.4 (C-2), 116.7 (C-8), 117.5 (C-4), 118.7 (C-4a), 129.4 (C-6), 129.7 (C-7), 132.4 (C-3), 138.4 (C-5), 154.5 (C-8a), 163.7 (C=O); ms: m/z 217 ($M^{+\bullet}$, 17), 203 (16), 202 (100), 161 (41), 87 (9).

Anal. Calcd. for $C_{13}H_{15}NO_2$: C, 71.91; H, 6.90; N, 6.44. Found: C, 71.73; H, 7.10; N, 6.31.

5-Formamido-2,2-dimethylchromene (**17**) (5-*N*-Hydroxyformimino-2,2-dimethylchromene).

This compound was obtained in 3% yield; ir: 3350, 3050, 1690, 1580 cm^{-1}; ^1H nmr: δ 1.18 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 5.66 (d, 1H, H-3, J = 10.0 Hz), 6.31 (d, 1H, H-4, J = 10.0 Hz), 6.58-6.66 (m, 2H, H-6, H-8), 7.03 (t, 1H, H-7, J = 8.0 Hz), 8.14 (d, 1H, OH, J = 8.2 Hz), 8.37 (d, 1H, N=CH, J = 8.2 Hz); ^{13}C nmr: δ 30.7 (C_2-CH_3), 76.2 (C-2), 115.1 (C-8), 116.8 (C-4), 125.9 (C-4a), 127.1 (C-6), 129.7 (C-7), 132.4 (C-3), 136.1 (C-5), 154.3 (C-8a), 164.3 (N=CH-OH); ms: m/z 204 ($(M+H)^+$, 14), 189 (13), 188 (100), 160 (21).

Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70.96; H, 6.40; N, 6.89. Found: C, 70.61; H, 6.08; N, 7.13.

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REFERENCES AND NOTES

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