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THE SYNTHESIS OF EUCOMIN AND (±)-EUCOMOL[1]

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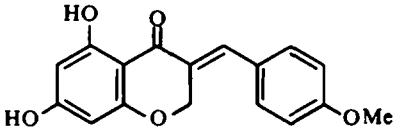
Abstract—5,7-Dihydroxychroman-4-one condenses with anisaldehyde in acetic anhydride to yield eucomin diacetate (5). Epoxidation of dibenzyleucomin followed by hydrogenation gave (±)-eucomol (2).

THE variety of naturally occuring oxygen heterocyclics has recently been further enriched by the isolation of eucomin (1) and (—)-eucomol (2) from the bulbs of *Eucomis bicolor* BAK. (Liliaceae) by Böhler and Tamm.[2]

These closely related compounds are benzylidene- and benzylchromanones and represent a new class of natural products.*



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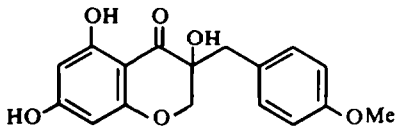

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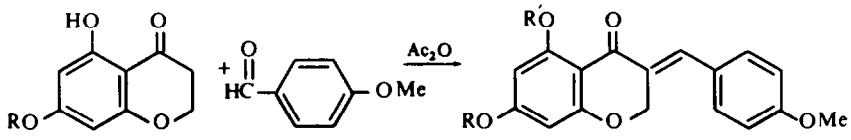
The structure of eucomin and (−)-eucomol, except for the absolute configuration of the latter, has been elucidated and eucomin dimethylether was synthesized.[2] In this paper we report the synthesis of eucomin (1) and racemic eucomol (2).

Although benzylidenechroman-4-ones are usually conveniently prepared by alkali-[3] or acid-catalysed[4, 5] condensation of chroman-4-ones with aromatic aldehydes, these methods failed with 5,7-dihydroxychroman-4-one. This is paralleled by the behaviour of phloracetophenone, which can not be converted directly to chalcones.[6] With chalcones this difficulty was circumvented by first glycosidation of phloracetophenone followed by alkaline condensation to the chalcone, and finally cleavage of the sugar moiety.[7] 5,6-Dihydroxychroman-4-one-7-β-D-glucoside (3) however failed to react with anisaldehyde or *p*-hydroxybenzaldehyde in sodium methoxide.

We have shown earlier,[8] that 2,3-dihydrobenzofuran-3-ones can be readily condensed with aromatic aldehydes to aurones by boiling acetic anhydride. This method

* The term "homo-isoflavones" introduced by Böhler and Tamm[2] has to be contested as 1 and 2 are not derived from isoflavones by the insertion of a C_1-unit and in contrast to isoflavones contain dihydropyrone rings.

proved to be useful with chroman-4-ones as well and prolonged boiling of 5,7-dihydroxychroman-4-one[9] (**4**) with anisaldehyde gave 5,7-diacetoxy-3-(4-methoxybenzylidene)-chroman-4-one, i.e. eucomin diacetate (**5**) in fair yield.

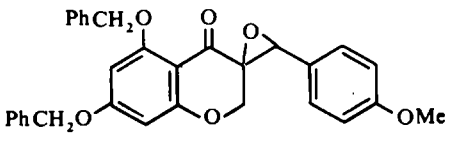


3: R = -glucosyl
4: R = H

5: R = R′ = Ac
6: R = Ac, R′ = H
7: R = R′ = CH_2Ph

Saponification of **5** gave 5,7-dihydroxy-3-(4-methoxybenzylidene)-chroman-4-one (**1**), identical with natural eucomin.* Careful acetylation of **1** gave the monoacetate (**6**) described by Böhler and Tamm.[2]

Benzylation of eucomin (**1**) in dimethylformamide gave dibenzyl eucomin (**7**), in acetone C-benzylation became predominant and the main product was 6-(or 8-)benzyl-5,7-dibenzyloxy-3-(4-methoxybenzylidene)-chroman-4-one. Treatment of **7** with alkaline hydrogen peroxide[4, 5] gave the epoxide **8**, which was smoothly converted by hydrogenation[10] to (±)3-(4-methoxybenzyl)-3,5,7-trihydroxychroman-4-one (**2**), racemic eucomol. The synthetic product has the same m.p. as (−)eucomol, and the IR spectra in chloroform are superimposable, but differ significantly in KBr.



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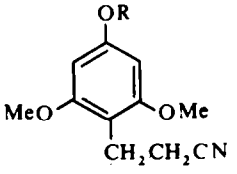

9: R = H
10: R = CH_2CH_2CN

The epoxide ring in **8** is easily opened by methanol and gives rise to 5,7-dibenzyloxy-(α,4-dimethoxybenzyl)-3-hydroxychroman-4-one.

5,7-Dihydroxychroman-4-one (**4**)[9] was prepared from 5,7-dihydroxychromone[11] by a new method involving hydrogenation in dimethylformamide in the presence of palladium-on-charcoal.

Fitton and Ramage reported the preparation of 7-methoxychroman-4-one from resorcinol monomethylether via cyanoethylation, hydrolysis of the cyanoether to the acid and ring closure.[12] An adaptation of this procedure to 3,5-dimethoxyphenol in

* We wish to express our gratitude to Prof. Ch. Tamm (Basel) for samples of natural eucomin and (−)eucomol.

order to obtain 5,7-dimethoxychroman-4-one was unsuccessful as C-cyanoethylation was preferred to O-cyanoethylation resulting in the formation of **9** and **10**. The structure of **10** was supported by its NMR spectrum and **9**, an unstable oil, was hydrolysed to the acid, so that it could be fully characterized.

EXPERIMENTAL

M.ps were determined on a Kofler hot-stage, NMR spectra were determined in $CDCl_3$ solns, with TMS as internal reference on a Varian A-60A spectrometer; infrared spectra were taken on a Perkin–Elmer 221 instrument.

5,7-Dihydroxychroman-4-one (**4**). 5,7-Dihydroxychromone[12] (4·0 g) in prehydrogenated dimethylformamide (60 ml) was hydrogenated in the presence of Pd-C (10%, 3 g) until the uptake of one equiv of H_2. The usual work-up and recrystallization from 70% aqueous MeOH afforded the chromanone (3·10 g, 77%), m.p. 234–235° (lit[10] 230°).

5,7-Diacetoxy-3-(4-methoxybenzylidene)-chroman-4-one; eucomin diacetate (**5**). Chromanone **4** (2·0 g) and anisaldehyde (1·65 ml) was refluxed in Ac_2O (30 ml) for 80 hr. Excess reagent was removed by steam distillation and the residue crystallized from MeOH (200 ml); orange needles (1·0 g, 24%), m.p. 152–154°; ν_{max} (KBr) 1780 (ester CO), 1670 (CO); NMR: δ, ppm, 2·28 and 2·40 (s, Ac), 3·83 (s, OMe), 5·32 (d, J = 2 Hz, C_8-H), 6·94 (d, J = 8·5 Hz, C_3,-H, C_5,-H), 7·23 (d, J = 8·5 Hz, C_2,-H, C_6,-H) and 7·77 (s, broad, =CH—). (Found: C, 66·4; H, 4·9. $C_{21}H_{18}O_7$ requires: C, 66·0; H, 4·7%).

5,7-Dihydroxy-3-(4-methoxybenzylidene)-chroman-4-one, synthetic eucomin (**1**). Saponification of **5** (0·60 g) with ethanolic alkali afforded after crystallization from MeOH eucomin as yellow needles (0·45 g), m.p. 200–201° (lit[2] 194–196°). Natural and synthetic specimens of **1** gave superimposable IR spectra (KBr); lack of material prevented mixed m.p. determination. (Found: C, 68·3; H, 4·7. $C_{17}H_{14}O_5$ requires: C, 68·4; H, 4·7%).

7-Acetoxy-5-hydroxy-3-(4-methoxybenzylidene)-chroman-4-one (**6**). Eucomin (0·2 g) was boiled with Ac_2O (5 ml) for 35 min. The usual work-up yielded **6** as pale yellow needles of m.p. 147–147·5° (lit[2] 146–147°). Ferric reaction in MeOH brown.

5,7-Dibenzyloxy-3-(4-methoxybenzylidene)-chroman-4-one (**7**). Eucomin (1; 2·0 g) benzylchloride (2·0 ml) and anhyd K_2CO_3 (6 g) was stirred in dimethylformamide (30 ml) at 100° for 5 hr. After steam distillation and recrystallization from acetone the pure dibenzyl ether was obtained as pale yellow prisms (1·5 g), m.p. 152–154°, ν_{max} (KBr) −1665 (CO) cm^{-1}; NMR: δ, ppm, 3·87 (s, OMe), 5·07 and 5·21 (s, $PhCH_2$), 5·28 (d, J = 2 Hz, 2-CH_2), 6·19 (d, J = 2 Hz, C_6-H), 6·29 (d, J = 2 Hz, C_8-H), 6·96 (d, J = 8·5 Hz, C_3,-H, C_5,-H), 7·40 (s, $C_6H_5CH_2$) and 7·85 (s, broad, —CH=). (Found: C, 77·9; H, 5·36. $C_{31}H_{26}O_5$ requires: C, 77·8; H, 4·7%).

6-(or 8-)-Benzyl-5,7-dibenzyloxy-3-(4-methoxy-benzylidene)-chroman-4-one. Eucomin (0·6 g), benzylchloride (1·0 ml) and anhyd K_2CO_3 (3 g) was refluxed with stirring in acetone (25 ml) until the starting material disappeared (60 hr). After steam distillation and recrystallization from acetone pale yellow needles of m.p. 185–186°, ν_{max} (KBr) 1670 (CO) cm^{-1}, NMR: δ, ppm, 3·86 (s, OCH_3), 4·02 (s, C-CH_2Ph), 5·04 and 5·08 (s, OCH_2Ph), 5·43 (d, J = 2 Hz, 2-CH_2), 6·38 (s, C_6-H or C_8-H), 6·99 (d, J = 8·5 Hz, C_3,-H), 7·12–7·65 (m, 17 H, C_2-H, C_6,-H, $C_6H_5CH_2$) and 7·92 (s, broad, —CH=). (Found: C, 80·2; H, 5·5. $C_{38}H_{32}O_5$ requires: C, 80·2; H, 5·7%).

5,7-Dibenzyloxy-3-(4-methoxybenzylidene)-3,α-oxido-chroman-4-one (**8**). To a soln of **7** (1·45 g) in MeOH-acetone (1:4, 150 ml) H_2O_2 (30%, 4·1 ml) and 2 N NaOH hydroxide (6·15 ml) was added. After stirring for 24 hr, the soln was filtered, evaporated and the residue crystallized from acetone-MeOH to give **8** as colourless four-cornered plates, m.p. 162–163°; NMR: δ, ppm, 3·79 (s, OMe), δ_A 4·39, δ_B 4·08 (AB system, J = 12·5 Hz, 2-CH_AH_B), 4·58 (s, —CH—O), 5·05 and 5·15 (s, OCH_2Ph), 6·12 (d, J = 2 Hz, C_6-H), 6·29 (d, J = 2 Hz, C_8-H), 6·96 (d, J = 8·5 Hz, C_3,-H, C_5,-H) 7·25 (d, partly overlapped, C_2,-H, C_6,-H) 7·30–7·70 (m, 15 H, $C_6H_5CH_2$). (Found: C, 75·2; H, 5·3. $C_{31}H_{26}O_6$ requires: C, 75·3; H, 5·31%).

5,7-Dibenzyloxy-3-(α,4-dimethoxybenzyl)-3-hydroxy-chroman-4-one. Epoxide **8** (100 mg) was boiled in MeOH (3 ml) with a trace of *p*-toluenesulfonic acid for 45 min. On cooling the product (61 mg) separated. Colourless prisms (from MeOH-acetone), m.p. 155–156°; λ_{max} 3450 (OH) and 1685 (CO) cm^{-1}; NMR: δ, ppm, 3·30 (s, α-OMe), 3·72 (s, 4-OMe), δ_A 4·05, δ_B 4·87 (AB-system, J = 11 Hz, 2-CH_AH_B), 4·48 (s, CH-OMe), 5·06 and 5·12 (s, OCH_2Ph), 6·20 (s, C_6-H, C_8-H), 6·77 (d, J = 9 Hz, C_3,-H, C_5,-H), 7·07 (d, J = 9 Hz, C_2,-H, C_6,-H), 7·33 and 7·39 (s, $C_6H_5CH_2$). (Found: C, 72·8; H, 6·0. $C_{32}H_{30}O_7$ requires: C, 73·0; H, 5·7%).

(±)3-(4-*Methoxybenzyl*)-3,5,7-*trihydroxy-chroman*-4-*one, synthetic* (±)-*euconol* (2). Epoxide **8** (220 mg) in EtOAc (20 ml) was hydrogenated with palladium oxide hydrate on barium sulfate catalyst.[13] The calculated amount of H_2 was absorbed in 2 min. The usual work-up and repeated recrystallization from benzene gave eucomol (80 mg) as colourless plates of m.p. 132–134·5°, (lit[2] for (−)-eucomol 134·5–135°), m.m.p. with (−)-eucomol 127–130°. ν_{max} ($CHCl_3$), 3350, 3270, 2900, 1620, 1595, 1515, 1480, 1460, 1390, 1300, 1270, 1160, 1120, 1075, 1030, 980, 950, 930 and 820 cm^{-1}; ν_{max} (KBr), 3350, 3220, 2900, 1640, 1610, 1520, 1485, 1465, 1390, 1280, 1240, 1210, 1160, 1125, 1090, 1075, 1030, 980, 950, 905, 870, 835, 800 and 730 cm^{-1}; (lit[2] for (−)-eucomol ν_{max} (KBr) 3450, 3380–3305, 1635, 1610, 1585, 1510, 1446, 1245 and 835 cm^{-1}).

3-[4-(2-*Cyanoethyl*)-3,5-*dimethoxyphenoxy*]*propionitrile* **10** *and* 3-(4-*hydroxy*-2,6-*dimethoxyphenyl*)-*propionitrile* **9**. 3,5-Dimethoxyphenol[14] (20 g) was refluxed in acrylonitrile (60 ml) with NaOMe (1·5 g) for 7 hr. The mixture was acidified with AcOH, distilled with steam to remove the excess of acrylonitrile and the product extracted with ether. The ethereal soln soon deposited some crystalline material (3·8 g), that was recrystallized from acetone to give **10** as colourless needles, m.p. 191–192°, ν_{max} 2900, 2700 (OCH_3), and 2280 (CN) cm^{-1}; NMR: δ, ppm, 2·11, 2·17, 2·23 (group of 3 sharp lines, 8H, CH_2), 3·81 (s, OMe) and 5·73 (s, C_2-H, C_6-H). (Found: C, 64·5; H, 6·2; N, 10·4. $C_{14}H_{16}N_2O_3$ requires: C, 64·6; H, 6·2; N, 10·8%). Evaporation of the ethereal soln, and distillation of the residue gave nitrile **9** as a colourless oil (15·2 g, 57%), $b.p._{0.5}$ 180–186°. (Found: N, 6·7, $C_{11}H_{15}NO_4$ requires: N, 6·8%).

3-(4-*Hydroxy*-2,6-*dimethoxyphenyl*) *propionic acid.* Nitrile **9** (1·0 g) was refluxed with a mixture of AcOH (8 ml) and conc HCl (6 ml) for 8 hr. After steam distillation the acid was separated and recrystallized from water. Colourless needles, m.p. 194–195°; ν_{max} 3300 (OH), 1710 (COOH) and 1435 (COOH) cm^{-1}; NMR: δ, ppm, (DMSO-d_6), 2·1–3·1 (m, 4H, CH_2CH_2), 3·78 (s, OCH_3); 6·17 (s, C_3-H, C_5-H), 9·39 (s, broad, Ar-OH) and 12·18 (s, broad, COOH). (Found: C, 58·3; H, 6·0. $C_{11}H_{14}O_5$ requires: C, 58·3; H, 6·23%).

5,7-*Dihydroxychroman*-4-*one*-7-β-*D-glucoside tetra-acetate.* To a soln of **4** (0·6 g) in acetone (8 ml), KOH aq (10%, 2·2 ml) and 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide (1·65 g) was added at 0°. The mixture was allowed to stand overnight, evaporated, the oily residue washed with water and repeatedly recrystallized from EtOH. Colourless long prisms (0·47 g, 36%), m.p. 166–167°. (Found: C, 53·8; H, 5·1. $C_{23}H_{26}O_{13}$ requires: C, 54·1; H, 5·1%).

5,7-*Dihydroxychroman*-4-*one*-7-β-*D-glucoside* (3). Saponification of glucosyl acetate (0·20 g) with NaOMe gave after the usual work-up and recrystallization from water the free glucoside as colourless needles of m.p. 232–234°. (Found: C, 52·5; H, 5·2. $C_{15}H_{18}O_9$ requires: C, 52·7; H, 5·3%).

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