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NATURAL CHROMONES—I

A TOTAL SYNTHESIS OF VISNAGIN

M. M. BADAWI and M. B. E. FAYEZ
National Research Centre, Dokki, Cairo, U.A.R.

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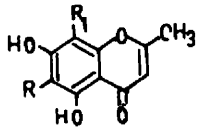
Abstract—A modified synthesis of the naturally occurring visnagin is reported. Starting from phloroglucin aldehyde, and building on the 2-methyl-γ-pyrone, 2-methyl-5,7-dihydroxy-6-formyl-chromone was obtained. Construction of the furan moiety was realized by a conventional method through the 7-carboxy-methoxy ether giving 5-norvisnagin which can be methylated to visnagin. Nuclear acylations in the chromone benzene ring are reported.

THE construction of linearly disposed furochromones, as well as furocoumarins, has been a subject of interest, chiefly on account of the synthesis of a range of natural products with established biological activity. Most of the known methods employed in the synthesis of visnagin[1–4] and khellin, the principal furochromone constituents of *Ammi visnaga* fruits,[5] were basically concerned with the initial elaboration of the appropriately constituted benzofuran derivative and the final construction of a 2-methyl-γ-pyrone on to it. Thus, in a number of syntheses, visnaginone and khellinone were the final products aimed at prior to the ultimate pyrone ring closure by the familiar Kostanecki-Robinson method.[6] In a modified synthesis, Dann *et al.*[7] realized a different 2-methyl-γ-pyrone ring construction through the use of β-chloro-crotonic acid methyl ester with an appropriate phenolic benzofuran derivative. An alternative approach to the synthesis of the furochromone nucleus consists in building a furan moiety on to a benzo-γ-pyrone. This method has so far been applied in syntheses of khellin and visnagin described by Seshadri *et al.*[4,8] using the 6-acetaldehyde derivative as key intermediate.

A particular difficulty in the synthesis of visnagin is the vulnerability of the 8-position in the chromone system to attack by reagents and the known[9] fact that migration of the Claisen type from a 7-allyloxy grouping also proceeds to this position. Consequently, Gruber and Horvath,[1] in the first total synthesis of visnagin—by the benzofuran route—started with a product protected in this position. Davies and

[1] W. Gruber and K. Horvath, *Monatsh.* **81**, 819 (1950).
[2] J. S. H. Davies and W. L. Norris, *J. Chem. Soc.* 3195 (1950).
[3] T. A. Geissman and E. Hinreiner, *J. Amer. Chem. Soc.* **73**, 782 (1951).
[4] R. Aneja, S. K. Mukerjee and T. R. Seshadri, *Tetrahedron* **3**, 230 (1958).
[5] H. Schmid, *Fortsch. Chem. org. Naturstoffe* **11**, 124 (1954).
[6] S. von Kostanecki and A. Rózycki, *Chem. Ber.* **34**, 102 (1901); S. von Kostanecki and L. Lloyd, *Ibid.* **34**, 2942 (1901).
[7] O. Dann and G. Illing, *Liebigs Ann.* **605**, 146 (1957); O. Dann and H. G. Zeller, *Chem. Ber.* **93**, 2829 (1960).
[8] R. Aneja, S. K. Mukerjee and T. R. Seshadri, *J. Sci. Ind. Research* **17B**, 382 (1958); *Chem. Ber.* **93**, 297 (1960).
[9] S. S. Chibber, A. K. Ganguly, S. K. Mukerjee and T. R. Seshadri, *Proc. Ind. Acad. Sci.* **A46**, 19 (1957).

Norris[2] and Geissman and Hinreiner,[3] using starting materials with no such protection, obtained mixtures which had to be resolved. In the present work, the construction of the furan on to a chromone nucleus by cyclization of a desired *o*-hydroxy-(*ω*-bromo)-acetophenone did not materialize. For although the 6-acetyl derivative (II) was prepared from the easily obtainable 2-methyl-5,7-dihydroxychromone (I) by a Friedel–Crafts condensation with acetic anhydride in the presence of zinc chloride, its bromination with N-bromosuccinimide led only to attack at the vacant 8-position to give III. It may be recorded that similar bromination of 2,4-dihydroxy-3,6-dimethoxyacetophenone led[10] only to nuclear attack. The constitution of II was proved by synthesis by an alternative route. Treatment of phloroacetophenone with ethyl acetoacetate in boiling diphenyl ether led to II in good yield; the reaction having involved the nonchelated hydroxyl in the formation of the *γ*-pyrone. When aluminium chloride was used in the Friedel–Crafts acylation of I, a diacetyl derivative (IV) was obtained in which both 6- and 8-positions were involved. That the acetyl group was indeed located at the 6-position in II was also evident from the fact that this substance, like the 6-formyl analogue (V), afforded the same trihydroxy derivative (VI) upon Dakin hydrogen peroxide oxidation.



I, $R = R_1 = H$

II, $R = COCH_3$, $R_1 = H$

III, $R = COCH_3$, $R_1 = Br$

IV, $R = R_1 = COCH_3$

V, $R = CHO$, $R_1 = H$

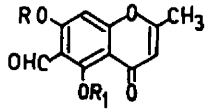
VI, $R = OH$, $R_1 = H$

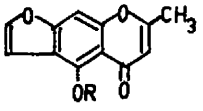
It was also thought that direct formylation of 2-methyl-5,7-dihydroxychromone (I) at the 6-position would give V from which a furan could be constructed in a conventional manner.[5,6] This method, however, was abandoned due to the formation of intractable mixtures or recovery of starting material despite many attempts to introduce the formyl group such as the use of esterified or partially esterified derivatives of I. This is in marked contrast to a corresponding synthesis of khellin[11] in which the 8-position is already substituted.

The desired 2-methyl-5,7-dihydroxy-6-formylchromone (V) was finally obtained

[10] D. M. X. Donnelly, R. M. Lowless and R. K. Wilson, *Chem. & Ind.* 1906 (1961).
[11] V. V. S. Murti and T. R. Seshadri, *Proc. Ind. Acad. Sci.* A30, 107 (1949).

from phloroglucin aldehyde by building on to it the 2-methyl-γ-pyrone through condensation with ethyl acetoacetate in an inert solvent such as diphenyl ether at its b.p. The reaction is a modification[12] of the Simonis synthesis[13] in which the condensation of phenols with β-ketonic esters in acid media normally gives coumarin derivatives and of the Mentzer[14] method in which the reaction is carried out at elevated temperatures without the use of condensing agent to lead exclusively to chromones. In this manner the requisite aldehyde group was secured in the 6-position and, at the same time, the need to protect the 8-position was obviated. It seems that the combined chelating effect of both the pyrone carbonyl and the aldehyde group (in V) was so pronounced that intensive treatment with methylating agents led only to etherification of the 7-hydroxyl, giving a product (VII) which was previously obtained[15] by a different route. Treatment of V with tosyl chloride also led to etherification of the same hydroxyl (VIII) and a subsequent treatment with methylating agent did not affect the 5-hydroxyl. It was preferred, therefore, to proceed first with the elaboration of the furan ring which was realised in a conventional manner. Treatment with ethyl bromoacetate afforded the partial ether (IX), saponification of which to give the acid (X) was followed by treatment with acetic anhydride containing sodium acetate to afford visnagin 5-0-acetate (XI). Mild saponification of the latter gave norvisnagin (XII) which was readily methylated to visnagin (XIII).





VII, $R=CH_3, R_1=H$

VIII, $R=$ Tosyl, $R_1=H$

IX, $R=CH_2COOC_2H_5, R_1=H$

X, $R=CH_2COOH, R_1=H$

XIV, $R=H, R_1=CH_3$

XI, $R=COCH_3$

XII, $R=H$

XIII, $R=CH_3$

The formation of the furan was also realized starting from 2-methyl-5-methoxy-6-formyl-7-hydroxychromone (XIV), an oxidation product[16] of visnagin, by following a parallel sequence (*viz.* V → IX → X → XIII) and afforded visnagin. An attempt to perform the cyclization directly with the ester (5-methyl ether of IX) using alkali[17] or magnesium methoxide[18] led only to polymeric products. This is presumably due

[13] K. B. Desai, K. N. Trivedi and S. Sethna, *J. M. S. Univ. Baroda* **4**, 1 (1955).
[13] W. Baker and R. Robinson, *J. Chem. Soc.* **127**, 1981, 2349 (1925).
[14] C. Mentzer, D. Molho and P. Vercier, *C.R. Acad. Sci. Paris* **232**, 1488 (1951); C. Mentzer and D. Pillon, *Ibid.* **234**, 444 (1952); *Bull. Soc. Chim. Fr.* 538 (1953).
[15] A. Mustafa, N. Starkovsky and E. Zaki, *J. Org. Chem.* **25**, 794 (1960).
[16] A. Schönberg, N. Badran and N. A. Starkovsky, *J. Amer. Chem. Soc.* **75**, 4992 (1953).
[17] Ch. B. Rao, G. Subramanyam and V. Venkateswarlu, *J. Org. Chem.* **24**, 685 (1959).
[18] R. A. Baxter, G. R. Ramage and J. A. Timson, *J. Chem. Soc.* S30 (1949).

to interaction of the 2-methyl with the formyl group which is known[19] to be a property of the 2-methylchromones.

EXPERIMENTAL

2-Methyl-5,7-dihydroxy-6-acetylchromone (II)

a. Finely powdered $ZnCl_2$ (freshly fused, 5 g) was dissolved in glacial acetic acid (5 ml) by heating at 135–140°. After the addition of acetic anhydride (5 ml) to the clear solution, 2-methyl-5,7-dihydroxychromone (m.p. 279–281°, 9 g) was added in one portion and the temp maintained at 140–145° for 75 min with frequent shaking. The reaction mixture was cooled and then poured on ice with stirring for 30 min and left to stand overnight. The solid which separated was crystallized from $CHCl_3$–EtOH to give 6 g of colourless needles, m.p. 205–207°. (Found: C, 61·79; H, 4·51. $C_{12}H_{10}O_5$ requires: C, 61·54; H, 4·30%.)

b. A solution of phloroacetophenone (m.p. 217–219°, 7 g) in ethyl acetoacetate (21 ml) containing 20 ml diphenyl ether was refluxed for 75 min. After cooling, ether was added and the solid formed was separated and washed twice with ether. Crystallization from $CHCl_3$–EtOH gave 4·6 g 2-methyl-5,7-dihydroxy-6-acetylchromone, m.p. and mixed m.p. 205–207°. The IR spectra of the two preparations were identical.

2-Methyl-5,7-dihydroxy-6,8-diacetylchromone (IV)

A suspension of 2-methyl-5,7-dihydroxychromone (1 g) in nitrobenzene (6 ml) was treated with anhydrous $AlCl_3$ (2 g) added portionwise while cooling until a clear solution resulted. Acetyl chloride (0·8 ml) was added dropwise while heating on a water bath. After 15 min, $AlCl_3$ was decomposed with ice–HCl aq mixture and nitrobenzene was removed by steam distillation. The solid which resulted upon cooling was crystallized from EtOH to give 0·8 g of colourless needles, m.p. 155–157°. (Found: C, 61·05; H, 4·44. $C_{14}H_{12}O_6$ requires: C, 60·87; H, 4·38%.)

Bromination of (II). A mixture of 2-methyl-5,7-dihydroxy-6-acetylchromone (1·1 g) and N-bromosuccinimide (1·2 g) in CCl_4 (20 ml) was refluxed for 1 hr. Removal of the solvent followed by crystallization of the residue from $CHCl_3$–EtOH afforded 0·9 g colourless needles, m.p. 194–196°. (Found: C, 45·99; H, 2·91; Br, 25·32. $C_{12}H_9O_5Br$ requires: C, 46·00; H, 2·87; Br, 25·56%.)

2-Methyl-5,6,7-trihydroxychromone (VI)

The 6-acetyl derivative (II, 1 g) was dissolved in 4% NaOH aq (10 ml) and 30% H_2O_2 (3 ml) was added to the ice-cold solution. The mixture was left in the cooling mixture for 6 hr with occasional shaking. After neutralization with acetic acid, the solid which formed was crystallized from EtOH to give 0·7 g yellowish plates which gave a green $FeCl_3$ reaction, m.p. 285–287°. The substance was identical (mixed m.p. and IR spectra) with the same product prepared, as described by Schönberg *et al.*,[20] by treatment of 2-methyl-5-methoxy-6-formyl-7-hydroxychromone with H_2O_2 as given above followed by demethylation. Reported[20] m.p. 284–286°.

The same product was also obtained by a similar treatment of 2-methyl-5,7-dihydroxy-6-formylchromone (0·5 g) with 30% H_2O_2 (2 ml) in 4% NaOH aq (5 ml) for 6 hr. After the usual work-up, 0·4 g VI was obtained, m.p. and mixed m.p. 285–287°.

2-Methyl-5,7-dihydroxy-6-formylchromone (V)

A solution of phloroglucin aldehyde (1 g) in ethyl acetoacetate (3 ml) and diphenyl ether (20 ml) was refluxed for 1 hr. After cooling and removal of the solvent by steam distillation, the product was extracted with ether and worked up. Crystallization from $CHCl_3$–EtOH gave yellow needles, m.p. and mixed m.p., with a sample prepared as described by Schönberg *et al.*,[16] 198–200°. Reported[16] m.p. 195°.

2-Methyl-5-hydroxy-6-formyl-7-tosyloxychromone (VIII)

A solution of V (5 g) in dry acetone (200 ml) containing anhydrous K_2CO_3 (20 g) and tosyl chloride (5 g) was refluxed for 12 hr. After the usual work-up, the product was crystallized from

[19] R. C. Elderfield, *Heterocyclic Compounds* Vol. 2; p. 257. Wiley, New York (1951).
[20] A. Schönberg, N. Badran and N. Starkovsky, *J. Amer. Chem. Soc.* 77, 1019 (1955).

$CHCl_3$–EtOH to afford canary yellow plates giving a wine red $FeCl_3$ reaction, m.p. 198–200°. (Found: C, 57·67; H, 3·85. $C_{18}H_{14}O_7S$ requires: C, 57·75; H, 3·74%.) Treatment of this substance with MeI under the same conditions given above and for prolonged reflux periods (e.g. 100 hr) led only to unchanged material. A similar treatment of V (0·5 g) with MeI (5 ml) in acetone (50 ml) solution containing anhydrous K_2CO_3 (3 g) required 120 hr reflux period to give, after the usual work-up, a yield of 0·5 g of VII, m.p. 254–256°. The substance gave a violet-red $FeCl_3$ reaction. Reported[16] m.p. 250°.

2-Methyl-5-hydroxy-6-formyl-7-carbethoxymethoxychromone (IX)

A solution of V (2 g) in dry acetone (200 ml) containing anhydrous K_2CO_3 (12 g) was treated with ethyl bromoacetate (15 ml) under reflux for 150 hr. The product, isolated in the usual manner, crystallized from $CHCl_3$–EtOH as colourless plates, m.p. 203–205°, giving a wine red $FeCl_3$ reaction. The substance gave a yellow solution upon treatment with uranyl acetate[15] and a heavy precipitate upon dilution. (Found: C, 58·95; H, 4·59. $C_{15}H_{14}O_7$ requires: C, 58·82; H, 4·61%.)

2-Methyl-5-hydroxy-6-formyl-7-carboxymethoxychromone (X)

A mixture of IX (0·5 g) and dil. HCl aq (1:1, 12 ml) was warmed on a water bath for 30 min. The solid which separated on cooling crystallized from acetic acid as colourless plates (0·4 g), m.p. 275–277° dec. (Found: C, 56·08; H, 3·89. $C_{13}H_{10}O_7$ requires: C, 56·12; H, 3·62%.)

Cyclization of (X). A mixture of X (0·5 g) and fused sodium acetate (1 g) in acetic anhydride (10 ml) was refluxed for 6 hr. The reaction mixture was poured onto ice-water and agitated for 10 min. After standing overnight, a product separated and was crystallized from EtOH to give 0·3 g creamy plates of 5-norvisnagin acetate (XI), m.p. 200–202°. The identity was established by mixed m.p. and comparison of the IR spectra. When the above experiment was conducted for a reflux period of 2 hr it gave nearly the same yield of 5-norvisnagin acetate along with a minute amount of 5-norvisnagin (XII) which was crystallized from EtOH, m.p. and mixed m.p. 156–158°. Reported[21] 156–158°.

5-Norvisnagin acetate (XI, 0·3 g) was hydrolysed by refluxing in dil. HCl aq (1:1, 6 ml) for 45 min. The product, which separated upon cooling, crystallized from EtOH as pale yellow plates (0·2 g), m.p. and mixed m.p. with 5-norvisnagin[21] 156–158°. Etherification with MeI in the usual manner afforded visnagin (XIII), m.p. and mixed m.p. with the natural product 139–140°. The IR spectra were identical.

2-Methyl-5-methoxy-6-formyl-7-carboxymethoxychromone

This substance was prepared first as described for IX by treatment of XIV (m.p. 189°, 10 g) with ethyl bromoacetate (12 ml) in dry acetone (150 ml) containing anhydrous K_2CO_3 (30 g) under reflux for 12 hr. The resulting ester, crystallizing from ether–light petroleum as colourless plates, m.p. 113–115°, was directly hydrolysed with HCl aq as described for X to give the free acid. This was crystallized from acetic acid to give colourless needles, m.p. 257–259°. (Found: C, 57·53; H, 4·33. $C_{14}H_{12}O_7$ requires: C, 57·54; H, 4·14%.)

Cyclization to visnagin (XIII). The acid from the previous experiment (300 mg) was treated with acetic anhydride (2 ml) containing anhydrous sodium acetate (0·6 g) and the mixture refluxed for 1·5 hr. Dilution followed by extraction of the product and crystallization from ether–light petroleum gave colourless needles of visnagin, m.p. 139–140° undepressed by the natural product. The IR spectra were identical in every detail.

An attempt to carry out the cyclization directly on the ester using magnesium methoxide[18] in absolute EtOH or by a brief treatment with 10% KOH aq[17] led only to reddish polymeric products with no definite m.p.

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[21] A. Schönberg and N. Badran, *J. Amer. Chem. Soc.* 73, 2960 (1951).