Tetrahedron, 1958, Vol. 3, pp. 230–235. Pergamon Press Ltd., London

SYNTHESIS OF BENZOFURAN DERIVATIVES—II

A NEW SYNTHESIS OF VISNAGIN

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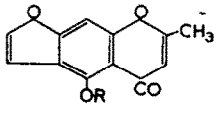
(*Received* 30 *December* 1957)

Abstract—Starting with 2-methyl-5:7-dihydroxychromone, an allyl group is introduced into the 6-position by Claisen migration of a 5-allyl ether. The initial protection of the 7-hydroxyl is best effected by tosylation. If the tosyl group is removed before Claisen migration and the C-allyl compound subjected to ozonolysis and ring closure, norvisnagin is obtained in a poor yield and can be methylated to visnagin. In an alternative method the tosyl group is removed just before ozonolysis. For this purpose the previous methylation of the 5-position is advantageous. This route gives visnagin directly in good yield.

IN part I[1] a new method of synthesis of benzopyronofurans was described. It consisted in building up a furan ring on to a pyrone system. The feasibility of the method was illustrated by the synthesis of a number of angular benzopyronofuran derivatives. Its suitability for the preparation of compounds of the linear type has now been examined, visnagin being taken as the typical example.

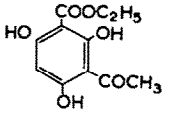
Visnagin is the major component of the seeds of *Ammi Visnaga*, an important plant drug. Its constitution was established by Späth and Gruber[2] as a linear chromonofuran derivative (Ia). The earliest synthesis was by Gruber and Horváth[3], who, starting with the ethyl ester of phloroacetophenonecarboxylic acid (II) built up a furan ring first, then removed the protecting carbethoxy group and finally closed the chromone ring. Later, Davies and Norris[4] and Geissman and Hinreiner[5] carried out the synthesis without the initial introduction of the carbethoxy group. Mixtures were naturally produced and had to be separated at several stages. Both methods involved a large number of steps and the final yield of visnagin was small.



I

(a) R = $-CH_3$

(b) R = $-H$



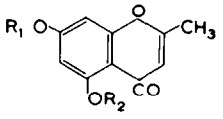
II

The synthesis in which the furan ring is built up last, may be more closely following the process of biosynthesis in plants. This could be expected to lead to a more efficient and a simpler route. In the present case the furan ring closure involves the 6-position and, since nuclear methylation of chromones and flavones[6] is definitely known to

[1] R. Aneja, S. K. Mukerjee and T. R. Seshadri *Tetrahedron* **2**, 203 (1958)
[2] E. Späth and W. Gruber, *Ber. Dtsch. Chem. Ges.* **74**, 1492 (1941).
[3] W. Gruber and K. Horváth, *Mh. Chem.* **81**, 819 (1950).
[4] J. S. H. Davies and W. L. Norris, *J. Chem. Soc.* 3195 (1950).
[5] T. A. Geissman and E. Hinreiner, *J. Amer. Chem. Soc.* **73**, 782 (1951).
[6] S. K. Mukerjee and T. R. Seshadri, *Proc. Ind. Acad. Sci.* A **38**, 207 (1953).

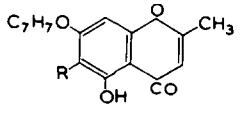
take place in the 6-position, nuclear allylation of 2-methyl-5:7-dihydroxychromone[7] was attempted; it gave only a resinous product. In this connection may be mentioned the similar experience of Bolleter *et al.*,[8] who reported that nuclear allylation of the same chromone with dimethylallyl bromide gives an extremely poor yield.

As an alternative method, Claisen migration was considered. The 7-allyl ether (IIIa) is easily made, but it is known[9] that the allyl group of this ether migrates to the vacant 8-position. On the other hand, the 5-allyl ether (IIIb) could be expected to suffer migration of the allyl group to the 6-position. But for the preparation of this ether (IIIb), the hydroxyl group in the 7-position has to be protected by means of a group capable of easy elimination at a later stage. The benzyl group was first employed; the 7-benzyl ether[7] of 2-methyl-5:7-dihydroxychromone (IIIc) was allylated in the 5-position and subjected to allyl migration. It proceeded satisfactorily to give the 6-allyl compound (IVa). Ozonolysis of this product or its 5-methyl ether, however, did not proceed smoothly. Alternatively, the acetate, 2-methyl-5-acetoxy-6-allyl-7-benzyloxychromone was treated with performic acid followed by hydrolysis with alkali. Though this gave a fair yield of the benzyloxydiol (IVb), which could be debenzylated by catalytic hydrogenation, subsequent fission of the diol (Va) by means of periodic acid did not succeed. Instead of the desired aldehyde (Vb), an iodine-containing product was formed and it was not further investigated.



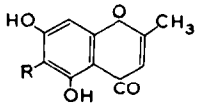
III

(a) $R_1 = -C_3H_5$; $R_2 = -H$
(b) $R_1 = -H$; $R_2 = -C_3H_5$
(c) $R_1 = -C_7H_7$; $R_2 = -H$



IV

(a) $R = -C_3H_5$
(b) $R = -CH_2 \cdot CHOH \cdot CH_2OH$



V

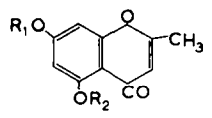
(a) $R = -CH_2 \cdot CHOH \cdot CH_2OH$
(b) $R = -CH_2 \cdot CHO$

The drawback in the foregoing method seemed to be the difficulty of removing the benzyl group in the presence of the allyl substituent. The benzoyl group appeared to be better for this purpose. The partial benzoate (VIa) of the dihydroxychromone was obtained in good yield, but, when it was heated under reflux with allyl bromide and potassium carbonate in acetone medium, besides the normal reaction, there was extensive debenzoylation and allylation of the 7-hydroxyl group thus set free. This route, therefore, became unworkable. Here may be mentioned the observation of Birch *et al.*[10], that deacetylation at the 7-position takes place under similar conditions of methylation.

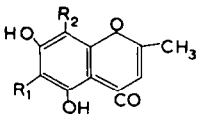
The above-mentioned difficulties were finally solved by working with the partial tosyl ester (VIb). It could be easily allylated to the 5-allyl ether (VIc), from which the tosyl group could be removed by hydrolysis. Subsequent Claisen migration gave the desired 2-methyl-6-allyl-5:7-dihydroxychromone (VIIa). This was definitely different from the isomeric 8-allylchromone (VIIb).[9] Ozonolysis and final ring

[7] K. C. Gulati, S. R. Seth and K. Venkataraman, *J. Chem. Soc.* 1766 (1934).
[8] A. Bolleter, K. Elier and H. Schmid, *Helv. Chim. Acta* **34**, 186 (1951).
[9] S. S. Chibber, A. K. Ganguly, S. K. Mukerjee and T. R. Seshadri, *Proc. Ind. Acad. Sci.* A **46**, 19 (1957).
[10] A. J. Birch, P. Elliot, S. K. Mukerjee, T. R. Rajagopalan, T. S. R. Seshadri and Varadarajan, *Aust. J. Chem.* **8**, 409 (1955).

closure yielded norvisnagin (Ib).[11] Yields in this series of experiments were good except at the ozonolysis stage.



VI



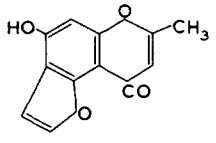
VII

(a) $R_1 = -COC_6H_5$; $R_2 = -H$ (a) $R_1 = -C_3H_5$; $R_2 = -H$

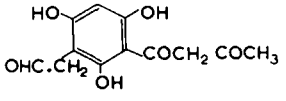
(b) R_1 = Tosyl ; $R_2 = -H$ (b) $R_1 = -H$; $R_2 = -C_3H_5$

(c) R_1 = Tosyl ; $R_2 = -C_3H_5$

Special mention should be made here that the product of the furan ring closure is a single entity, in which cyclisation has proceeded through the 7-hydroxyl group. The alternative ring closure involving the 5-hydroxyl group did not seem to proceed to any detectable extent, indicating that the 5-hydroxyl is unreactive, as is usually expected, owing to chelation. This observation appears to have an important bearing in regard to the mechanism of the ring isomeric change that visnagin undergoes when boiled with hydriodic acid.[12] Besides demethylation, the furan ring undergoes a shift to yield nor*iso*visnagin (VIII). This result would appear to be a contradiction of what has been mentioned above, because it could be considered to be due to the opening of only the furan ring and re-closing with the 5-hydroxyl group of the chromone. In fact the reaction seems to involve the simultaneous opening of the pyrone ring also. At this stage the furan ring closure could take place in the alternative direction, involving the 6-position of the diketone (IX), followed by re-formation of the pyrone ring.



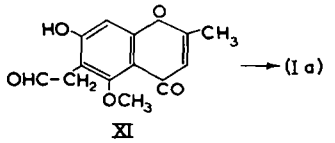
VIII



IX

By following a different sequence of the above experiments, it has been possible to obtain visnagin in much better yield. Claisen migration of the allyloxytosyloxychromone (VIc) proceeds in excellent yield. The tosyl group could not be removed from this ester (Xa) even by prolonged treatment with cold alkali. However, its 5-methyl ether (Xb), prepared readily by reaction with methyl iodide, underwent smooth detosylation to yield 2-methyl-5-methoxy-6-allyl-7-hydroxychromone (Xc).

X



XI

(a) R_1 = Tosyl ; R_2 = H

(b) R_1 = Tosyl ; $R_2 = -CH_3$

(c) R_1 = H ; $R_2 = -CH_3$

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

[12] J. R. Clark, G. Glaser and A. Robertson, *J. Chem. Soc.* 2260 (1948).

The subsequent stages of ozonolysis and ring closure of the 6-acetaldehydochromone (XI) afforded visnagin in good yield.

EXPERIMENTAL

2-Methyl-5-allyloxy-7-benzyloxychromone. On heating under reflux a solution of 2-methyl-5-hydroxy-7-benzyloxychromone[7] (3 g) in dry acetone (150 ml) containing excess of allyl bromide (3 ml) and potassium carbonate (6 g) for 35 hr, the crude allyl ether was obtained as a brown viscous liquid. Purification was effected by allowing a solution of it in benzene to percolate through a column of alumina (15 g) and eluting the column with light petroleum (400 ml, boiling range 40–60°). Evaporation of the eluate gave the allyl ether (3·2 g), which crystallised as colourless plates from dilute ethanol, m.p. 91–92° (Found: C, 74·4; H, 5·4. $C_{20}H_{18}O_4$ requires C, 74·6; H, 5·6 per cent).

2-Methyl-5-hydroxy-6-allyl-7-benzyloxychrome (IVa). The allyloxychromone (2 g) was heated under reduced pressure at 190–195° for 1½ hr. Crystallisation of the cold melt from ethanol after treatment with Norit yielded the migration product (1·9 g) as colourless needles, m.p. 129–130°, which gave a violet colour with ferric chloride (Found: C, 74·1; H, 5·8. $C_{20}H_{18}O_4$ requires C, 74·6; H, 5·6 per cent). The acetate crystallised from dilute methanol as colourless prisms m.p. 132–133°.

2-Methyl-5-methoxy-6-allyl-7-benzyloxychromone. Methylation of the 5-hydroxychromone (IVa) (0·5 g) with excess of methyl iodide and potassium carbonate (2 g) in boiling acetone (50 ml) for 50 hr yielded the methyl ether (0·5 g) as colourless prismatic rods from ethanol, m.p. 92–93° (Found: C, 74·6; H, 6·4. $C_{21}H_{20}O_4$ requires C, 75·0; H, 6·0 per cent).

2-Methyl-5-hydroxy-6-(βγ-dihydroxypropyl)-7-benzyloxychromone (IVb). The acetate of 2-methyl-5-hydroxy-6-allyl-7-benzyloxychromone (0·5 g) in formic acid (10 ml) maintained at 35° was treated dropwise with an excess of 30% hydrogen peroxide (0·4 ml). After 4 hr the mixture was diluted with water, excess of peroxide was destroyed by adding a trace of 10% palladised charcoal and the solution was extracted with chloroform. The extract was washed with sodium bicarbonate solution and evaporated, and the residual glassy solid was hydrolysed by being kept in contact with 2% methanolic sodium hydroxide at 50° for 15 min. Acidification and crystallisation of the product from dilute methanol yielded the diol (0·25 g) as colourless short needles, m.p. 159–160°, which gave a violet colour with ferric chloride (Found: C, 67·6; H, 6·0. $C_{20}H_{20}O_6$ requires C, 67·4; H, 5·6 per cent).

2-Methyl-5:7-dihydroxy-6-(βγ-dihydroxypropyl)chromone (Va). A methanolic solution (20 ml) of the above benzyloxychromone (250 mg) was hydrogenated in the presence of 1% palladised charcoal (250 mg) until 1 mole of the gas had been absorbed. Evaporation of the filtered solution yielded the diol (Va) (150 mg). It crystallised as colourless rhombohedral plates from dilute ethanol, m.p. 201–202°, and gave a violet colour with ferric chloride (Found: C, 58·8; H, 4·7. $C_{13}H_{14}O_6$ requires C, 58·6; H, 5·3 per cent).

2-Methyl-5-hydroxy-7-benzoyloxychromone (VIa). Benzoyl chloride (5 ml) was added to a solution of 2-methyl-5:7-dihydroxychromone (5 g) in 10% aqueous sodium carbonate (200 ml) and the mixture was shaken at room temperature for 1 hr. The granular precipitate of the partial benzoate (7 g) was collected. On crystallisation from ethanol after treatment with Norit it was obtained as pale-yellow

plates, m.p. 130–131°, and it gave a violet colour with ferric chloride (Found: C, 69·0; H, 4·4. $C_{17}H_{12}O_5$ requires C, 68·9; H, 4·1 per cent).

2-*Methyl*-5-*hydroxy*-7-*tosyloxychromone* (VIb). 2-Methyl-5:7-dihydroxychromone (12 g) was heated under reflux with toluene-*p*-sulphonyl chloride (14·1 g) and potassium carbonate (30 g) in dry acetone (1200 ml) for 6 hr; the tosyl ester (19·5 g) crystallised from a mixture of chloroform and ethanol as pale-yellow rectangular prisms, m.p. 141–142°, which gave a bluish-red colour with ferric chloride (Found: C, 59·1; H, 4·4. $C_{17}H_{14}O_6S$ requires C, 59·0; H, 4·0 per cent). The mother-liquor deposited, on concentration and cooling, light-yellow tablets (0·5 g) of 2-methyl-5:7-ditosyloxychromone, m.p. 130–131° (Found: C, 57·8; H, 4·1. $C_{24}H_{20}O_8S_2$ requires C, 57·6; H, 4·0 per cent).

2-*Methyl*-5-*allyloxy*-7-*tosyloxychromone* (VIc). On heating under reflux the ester (VIb) (3 g) for 8 hr with allyl bromide (3·5 ml) and potassium carbonate (10 g) in dry acetone, the ether ester (VIc) (3·5 g) was obtained, colourless prisms from ethanol, m.p. 148–149° (Found: C, 62·3; H, 5·2. $C_{20}H_{18}O_6S$ requires C, 62·2; H, 4·7 per cent).

2-*Methyl*-7-*hydroxy*-5-*allyloxychromone* (IIIb). The tosyl ester (VIc) (10 g) in ethanol (300 ml) was mixed with 5% aqueous sodium hydroxide solution (200 ml). After 4 hr at room temperature, the mixture was diluted and extracted with ether to remove any unhydrolysed ester. The clear alkaline solution was acidified and extracted with ethyl acetate, and the extract was washed twice with aqueous sodium bicarbonate solution. Concentration of the ethyl acetate solution deposited the hydroxychromone (IIIb) (5 g), which crystallised from a mixture of ethyl acetate and ethanol as colourless rectangular prisms, m.p. 202–203° (Found: C, 67·2; H, 5·4. $C_{13}H_{12}O_4$ requires C, 67·2; H, 5·2 per cent).

2-*Methyl*-5:7-*dihydroxy*-6-*allylchromone* (VIIa). When the above 5-allyloxychromone (1 g) was heated at 200–205° under reduced pressure and the cooled migration product was crystallised from ethanol after treatment with Norit the dihydroxyallylchromone (0·9 g) was obtained as colourless plates, m.p. 227–230° (Found: C, 67·5; H, 5·6. $C_{13}H_{12}O_4$ requires C, 67·2; H, 5·2 per cent). It gave a violet colour with ferric chloride and a diacetate, as colourless rectangular plates from ethanol, m.p. 202–203°.

Ozonolysis of (VIIa). A stream of 3% ozonised oxygen (50 ml/min) was passed through a cooled (5°) solution of the dihydroxyallylchromone (VIIa) (300 mg) in formic acid (45 ml) for 70 min. The solution was set aside at room temperature for 1/2 hr and then stirred in an atmosphere of hydrogen in the presence of 1% palladised charcoal (0·6 g) until 1 mole of the gas had been absorbed (2 hr). The filtered and diluted solution was extracted with chloroform, and the extract was washed several times with dilute sodium bicarbonate solution and evaporated. The residual glassy solid was a mixture and could not be crystallised. It gave a positive Tollen's test and a 2:4-dinitrophenylhydrazone, which after two crystallisations from ethanol formed yellow needles, m.p. 215° (dec.) (Found: C, 52·0; H, 3·6. $C_{18}H_{14}O_8N_4$ requires C, 52·2; H, 3·4 per cent).

Cyclisation to norvisnagin (Ib). The glassy residue obtained above was treated with orthophosphoric acid (5 ml) at 100° for 10 min and then poured into cold water. The separated solid was extracted with chloroform and the extract was dried and chromatographed on a column of activated alumina (10 g). Elution of the column

with more chloroform and evaporation of the eluate yielded norvisnagin (50 mg), pale-yellow plates from ethanol, m.p. and mixed m.p. 156–157°, which gave a green colour with ferric chloride.

Further elution of the column with ethanol yielded 2-methyl-5:7-dihydroxy-6-propylchromone (60 mg), which formed colourless plates from ethyl acetate, m.p. 210–212°, undepressed by admixture with an authentic sample of the same prepared by the catalytic hydrogenation of the 6-allylchromone (VIIa) (Found: C, 67·1; H, 6·5. $C_{13}H_{14}O_4$ requires C, 66·7; H, 6·0 per cent).

2-*Methyl-5-hydroxy-6-allyl-7-tosyloxychromone* (Xa). This was obtained by the Claisen migration of 2-methyl-5-allyloxy-7-tosyloxychromone (VIc) (1 g) at 190–195° under reduced pressure for 1½ hr; this allylchromone (0·95 g) formed colourless hexagonal plates from ethanol after treatment with Norit, m.p. 129–130°, and gave a violet colour with ferric chloride (Found: C, 62·2; H, 4·7. $C_{20}H_{18}O_6S$ requires C, 62·2; H, 4·7 per cent).

2-*Methyl-5-methoxy-6-allyl-7-tosyloxychromone* (Xb). Methylation of the 5-hydroxychromone (Xa) (0·9 g) by heating it under reflux with excess of methyl iodide (1 ml) and potassium carbonate (2 g) in acetone solution was complete in 16 hr. The methyl ether (0·9 g) crystallised from ethanol as colourless rectangular prisms, m.p. 111–112° (Found: C, 63·5; H, 5·1. $C_{21}H_{20}O_6S$ requires C, 63·0; H, 5·0 per cent).

2-*Methyl-5-methoxy-6-allyl-7-hydroxychromone* (Xc). A mixture of the above tosyl ester (0·5 g) in ethanol (30 ml) and 10% aqueous sodium hydroxide solution (30 ml) was kept at room temperature for 3 hr, diluted with water and extracted with ether to remove any unhydrolysed ester. Acidification of the clear alkaline solution yielded the 7-hydroxy-6-allylchromone (0·3 g), colourless rhombic plates from ethanol, m.p. 220–221° (Found: C, 68·2; H, 5·8. $C_{14}H_{14}O_4$ requires C, 68·3; H, 5·7 per cent).

Ozonolysis of (Xc). A stream of 2·5% ozonised oxygen (50 ml/min) was bubbled through a cooled (5°) formic acid (20 ml) solution of the hydroxyallylchromone (Xc) (300 mg) for 45 min. After the solution had been set aside for ½ hr at room temperature, it was hydrogenated in the presence of 10% palladised charcoal (0·2 g) until 1 mole of hydrogen had been absorbed. When the solvent was removed from the filtered solution by distillation under reduced pressure and the residual brownish glass was treated in ethanolic solution with 2:4-dinitrophenylhydrazine hydrochloride, the 2:4-dinitrophenylhydrazone of the 6-acetaldehydochromone (XI) was obtained as yellow needles from ethanol, m.p. 255–257° (Found: C, 52·9; H, 3·8. $C_{19}H_{16}O_8N_4$ requires C, 53·3; H, 3·8 per cent).

Cyclisation to visnagin (Ia). The crude actaldehydochromone (from 300 mg of the allylchromone (Xc)) was heated with a mixture of orthophosphoric acid (3 ml) and phosphorus pentoxide (3 g) at 100° for 20 min, and the resulting deep green solution was cooled and poured into ice–water. The light-brown solid that separated was extracted with benzene, and the extract was dried and allowed to percolate through a short column of alumina (3 g); the column was then washed with more benzene. Evaporation of the eluate and the washings yielded visnagin (200 mg), m.p. and mixed m.p. 139–140°.