NUCLEAR OXIDATION IN FLAVONES AND RELATED COMPOUNDS

Part XXVII. A New Synthesis of Norwogonin and Its Methyl Ethers

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From the results obtained in previous parts1–5 of this series, it has been established that the two stage oxidation process is definitely satisfactory for nuclear ortho-oxidation in flavones and related compounds. In these particular cases, no para position is free to undergo this oxidation. However, when in other cases a para position should be free, as already stated, a general consideration of the reactions involved would indicate that the method should be available for para oxidations also. No experiments have so far been done in the flavone series to test this point. Further, when an ortho as well as a para position are available, how this two stage process would function required careful investigation. It was also noticed that there was considerable difference6 between 3-methoxy-7-hydroxy flavone and 7-hydroxy flavone in their reaction with hexamine and in their direct oxidation with alkaline persulphate. The yields in both the reactions were considerably higher with 3-methoxy-7-hydroxy flavone. The apparent influence of the methoxyl group in enhancing yields had to be examined, using other examples. Experiments carried out with reference to all these points are discussed in this paper.

(i) Oxidation of Tectochrysir—To test the feasibility of the two stage oxidation process for para oxidation, tectochrysin (I) was chosen as a suitable example. It contains a hydroxyl in the 5-position which can activate both the 6-(ortho) and the 8-(para) positions. There are many simpler examples in which both the ortho and para positions are activated by a phenolic hydroxyl group. Phenol on treatment with formalin and alkali yields both saligenin and p-hydroxy benzyl alcohol.7 Similarly salicylic acid when boiled with hexamine in acetic acid medium gives both the 3 and 5-aldehyde salicylic acids.8

It is now found that when tectochrysin (I) is condensed with hexamine in glacial acetic acid solution a single aldehyde (II) is obtained in 60% yield. The orientation of the aldehydo group has been determined as para.
to the hydroxyl by treating the compound with alkaline hydrogen peroxide, when it is converted to isowogonin (III). The identity of (III) has been confirmed by further methylation to 5:7:8-trimethoxy flavone. It is therefore established that the two stage process is available for para oxidations also in flavones and there is preferential activity of the 8-(para) position over the 6-(ortho). Incidentally a new synthesis of isowogonin is also effected. It should be noted, however, that in this instance of Dakin's reaction forming a quinol, the yield is rather low.

(ii) 5-O-Methyl chrysin.—It has been definitely established through experiments with flavones and chromones, that a 7-hydroxyl always activates the 8-position in the hexamine reaction. Murti and Seshadri found that even when the 8-position is occupied, a 7-hydroxyl does not activate the 6-position in this reaction. Experiments now carried out support these conclusions. 5-O-Methyl chrysin (VI, R=CH₃), isomeric with 7-hydroxy-3-methoxy flavone, is chosen in order to further investigate the activating influence of a methoxyl group. It is a new methyl ether of chrysin which was first obtained by Zemplen, et al. by the methylation and hydrolysis of toringin, a 7-glucoside of chrysin. The attempts of the above authors to synthesise it starting from 2-methyl phloracetophenone were unsuccessful. The unreliability of this method has already been commented upon. It has now been made by the methylation of 7-O-benzyl chrysin (IV) to 7-O-benzyl-5-O-methyl chrysin (V) and subsequent debenzylation. The hexamine reaction proceeds satisfactorily with (VI, R=CH₃) giving the 8-aldehyde (VII, R=CH₃) in 65% yield which is comparable to the yield (70%) of the aldehyde from 7-hydroxy-3-methoxy flavone. It may be noted here that 7-hydroxy flavone provides only a 40% yield of the corresponding aldehyde. The aldehyde (VII) is converted by Dakin's reaction into 7:8-dihydroxy-5-methoxy flavone (VIII, R = CH₃), a second isomer of wogonin, now named allowogonin. The constitution of (VIII) is proved by methylation to 5:7:8-trimethoxy flavone. These experiments, therefore, confirm the favourable influence of a methoxyl group in the hexamine reactions.
(iii) Chrysin.—It has been shown in the above paragraphs that the hydroxyl in the 5-position, and that in the 7-position both activate the 8-position. The combined influence of both the 5- and 7- hydroxyls has been shown to be favourable in the case of persulphate oxidations. This point has now been tested using the aldehyde method. Chrysin (VI, R = H) is an appropriate example for this purpose. It yields, as expected, the aldehyde (VII, R=H) in 90% yields. It is converted into norwogonin (VIII, R=H) by alkaline hydrogen peroxide; the yields in this reaction are again low probably due to the presence of a quinol structure in the final product. However this constitutes another synthesis of norwogonin.

EXPERIMENTAL

Chrysin and tectochrysin required for these experiments were prepared by the procedure recently described by Rao, Rao and Seshadri. Tectochrysin aldehyde (II).—Tectochrysin (1 g.) was dissolved in glacial acetic acid (20 c.c.) and heated on a boiling water-bath with hexamine (3 g.) for six hours. The solution which was pale red at the beginning turned slowly brown. To the hot solution was added boiling hydrochloric acid (1:1, 30 c.c.) and the mixture allowed to cool. On dilution with water (200 c.c.) a sticky solid separated out. More of it was formed when the solution was neutralised with sodium hydroxide. It slowly changed to a bright yellow powder on stirring well. It was filtered and washed with water. On crystallisation from a mixture of alcohol and ethyl acetate, it separated in the form of short yellow needles which did not melt below 340°. Yield 0.6 g. (Found: C, 68·6, H, 4·4; C_{12}H_{15}O_{6} requires C, 68·9, H, 4·1%). It was soluble in alcohol and acetic acid and sparingly soluble in ethyl acetate,
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benzene and acetone. It gave an orange red colour with alcoholic ferric chloride. The dinitrophenylhydrazone of the aldehyde crystallised from alcohol as dark red prisms and melted at 160-61° (decomp.).

Isowogonin (III).—The above aldehyde (1 g.) was dissolved in a mixture of pyridine (40 c.c.) and sodium hydroxide (3.7 c.c. of 1 N) and 6% hydrogen peroxide (5 c.c.) added slowly to the solution kept at 40° and with a stream of nitrogen passing through the flask to displace air. After allowing to stand at this temperature for 30 minutes, the solution was cooled and acidified. The pale brown solid product was filtered, washed with water and crystallised from ethyl acetate, when it came out as bright yellow needles melting at 234-35°, alone or in admixture with an authentic sample of isowogonin. Yield 0.2 g. In its colour reactions and other properties it was identical with isowogonin.

On methylation with dimethyl sulphate and anhydrous potassium carbonate in dry acetone medium, it yielded 5: 7: 8-trimethoxy flavone, m.p. 167-68°.

7-O-Benzyl-5-O-methyl chrysin (V).—7-O-Benzyl chrysin (1.5 g.) was dissolved in dry acetone (200 c.c.) and refluxed with dimethyl sulphate (0.7 c.c.) and potassium carbonate (10 g.) for 18 hours. Acetone was distilled off and water added to the residue and filtered. The undissolved pale brown solid, on crystallisation from benzene-petroleum ether mixture came out as colourless rectangular rods melting at 184-85°. It did not give any colour with alcoholic ferric chloride. Yield 1.3 g. (Found: C, 76.7, H, 5.1; C_{23}H_{18}O_{4} requires C, 77.1, H, 5.0%).

5-O-Methyl chrysin (VI, R=CH_{3}).—The above compound (V) (1 g.) was dissolved in glacial acetic acid (20 c.c.) and concentrated hydrochloric acid (14 c.c.) added and the mixture kept in a boiling water-bath for one hour. It was then diluted with water (100 c.c.) and the solid that separated out was filtered. Yield 0.5 g. On crystallisation from alcohol, it came out as thin colourless rhombic plates melting at 278-79°. It did not give any colour with alcoholic ferric chloride and dissolved in alkali to give a pale yellow solution. (Found: C, 71.2, H, 4.5; C_{18}H_{15}O_{4} requires C, 71.6, H, 4.5%).

5-O-Methylchrysin-8-aldehyde (VII, R=CH_{3}).—5-O-Methyl chrysin (VI) (2 g.) was heated on a boiling water-bath with glacial acetic acid (40 c.c.) and hexamine (6 g.) for 6 hours. Boiling hydrochloric acid (1: 1, 40 c.c.) was added to the hot brown solution. On cooling a pale yellow crystalline solid separated out. The solution was diluted with water and the precipitated solid filtered off. Yield 1.3 g. It crystallised from alcohol containing
a few drops of acetic acid as small pale yellow needles, m.p. 295° (decomp.). It gave a red colour with alcoholic ferric chloride. (Found: C, 68.7, H, 4.4; C₁₇H₁₂O₅ requires C, 68.9, H, 4.1%.)

The dinitro-phenylhydrazone of the aldehyde, prepared by heating an alcoholic solution of the substance with dinitrophenylhydrazine, melted at 172–73° (decomp.).

7: 8-Dihydroxy-5-methoxy flavone (Allowogonin) (VIII, R=CH₃).—The above aldehyde (0.5 g.) was dissolved in pyridine (25 c.c.) and aqueous sodium hydroxide (2 c.c. of 1 N). To the cooled solution was added hydrogen peroxide (3 c.c. of 6%) drop by drop, with shaking. It was left at room temperature for 2 hours and then acidified with ice-cold hydrochloric acid. The greenish yellow solid product was filtered and washed with water. Ether extraction of the filtrate gave some more of the substance. Yield 0.3 g. On crystallisation from rectified spirits, 7: 8-dihydroxy-5-methoxy flavone separated as pale yellow, long fine needles melting at 132°. It gave a greenish brown colour with alcoholic ferric chloride and a reddish brown solution in aqueous sodium hydroxide. (Found: C, 67.3, H, 4.6; C₁₆H₁₂O₅ requires C, 67.6, H, 4.2%).

On methylation with excess of dimethyl sulphate and potassium carbonate in dry acetone medium, it yielded 5: 7: 8-trimethoxy flavone melting at 167-68°. The mixed melting point with an authentic sample of the trimethyl ether was not depressed.

5: 7-Dihydroxy-flavone-8-aldehyde (VII, R=H).—Chrysin (1 g.) was dissolved in glacial acetic acid (20 c.c.) and heated with hexamine (3 g.) on a boiling water-bath. The solution which was originally red, turned deep reddish brown and after two hours began to deposit a yellow solid. The heating was continued for another four hours and the hot solution mixed with boiling hydrochloric acid (30 c.c.) (1: 1). It was then cooled and diluted with water (100 c.c.) and the bright yellow solid filtered. Yield 0.9 g. When crystallised from acetic acid, it came out as yellow rectangular plates which did not melt below 350°. It gave an orange colour with alcoholic ferric chloride, was insoluble in alcohol and benzene and very sparingly soluble in ethyl acetate and acetone. (Found: C, 67.9, H, 3.9; C₁₆H₁₀O₅ requires C, 68.1, H, 3.5%).

The dinitro phenylhydrazone prepared by refluxing an acetic acid solution of the aldehyde with alcoholic dinitrophenyl-hydrazine for 2 hours, melted at 314° (decomp.).

5: 7: 8-Trihydroxy flavone (Norwogonin) (VIII, R=H).—The above aldehyde (1 g.) was dissolved in pyridine (30 c.c.) and aqueous sodium hydroxide
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(3.7 c.c. of 1 N) and the solution was cooled to 10°. Hydrogen peroxide (6 c.c. of 6%) was added drop by drop when the red colour of the solution changed to deep brown. After 20 minutes, it was acidified and the brown solid filtered. When twice crystallised from ethyl acetate-petroleum ether mixture, it separated as golden yellow rectangular plates and prisms melting at 258-59°, alone or when mixed with an authentic sample of norwogonin. Yield 0.15 g.

SUMMARY

(1) Chrysin, (2) tectochrysin and (3) 5-O-methyl chrysin are subjected to the two stage oxidation process. All of them give good yields of the corresponding 8-aldehydes. In (2) the 8-position (para) is predominantly more reactive than the 6-position (ortho). In (1) and (3) the favourable influence of a hydroxyl and a methoxyl in the 5-position is exerted. The Dakin's reaction gives poor yields if the product is a quinol and good yields if it is a catechol. Experiments with (1) and (2) lead to the conclusion that the two stage method is available for para oxidations though the yields are poor.

REFERENCES

5. ———— . . Ibid., 1949, 30, 12.
6. Rangaswami and Seshadri . . Ibid., 1939, 9, 7.
    Narasimhachari, Row and Seshadri . . Ibid., 1948, 27, 37.