Synthesis of New Furobenzoxazole and Furoflavone Derivatives

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The synthesis of visnaginone-oxime (2a) and khellinone-oxime (2b) is reported. Beckmann rearrangement of 2a and 2b using different cyclising agents was studied. Structure assignment for the produced benzoxazole derivatives and benzisoxazole derivatives was confirmed by chemical and spectral evidences. Utilization of visnaginone (1a) and khellinone (1b) for the synthesis of new furoflavone derivatives was also undertaken.

It is well known that both nitrogen [1] and oxygen [2] heterocycles are eminent in the field of pharmaceutical chemistry. Compounds containing both types of heterocycles, particularly the furobenzoxazoles, and furobenzisoxazoles are of high biological importance and find wide applications as analgesic, antiinflammatory, muscle relaxant, bactericide as well as fungicide [3]. During our investigations in the benzo-furan series [4], it appeared now of interest to undertake the synthesis of some new furobenzoxazole (3) and furobenzisoxazoles (5) derived from visnaginone (1a) and khellinone (1b) respectively. This was achieved by condensing 1a and 1b with hydroxylamine, followed by cyclizing the oximes 2a and 2b so formed, under the conditions of Beckmann rearrangement. Thus, treatment of the oximes 2a and 2b with pyridine hydrochloride at 100 °C for 20 min, gave rise to 4-methoxy-

[Diagram of structures]

2-methylfuro[3,2-f]benzoxazole (3a) and 4,8-dimethoxy-2-methylfuro[3,2-f]benzoxazole (3b), respectively. Compound 3a was also obtained upon treatment of the oxime (2c), derived from visnaginone methyl ether (1c) with pyridine hydrochloride. A mixture of the oxazole (3a) and the anilide (4) was obtained upon using hydrogen chloride gas in glacial acetic acid in the cyclization of visnaginone oxime (2a). Similar treatment of the khellinone oxime (2b) yielded the benzoxazole (3b), however, as the sole reaction product.

The structure of the oxazole (3a) was confirmed by: (a) it is insoluble in dilute aqueous alkali and gives no colour reaction with alcoholic ferric chloride solution. (b) The IR spectrum of 3a showed two bands at 1160 cm⁻¹ and 1060 cm⁻¹ due to the in-plane bending vibrations of the α- and β-hydrogen atoms of the furan ring [5]. The bands in the 1625–1510 cm⁻¹ region are associated with the C=C (aromatic) and C=N (oxazole) vibrations [6, 7]. The band at 1375 cm⁻¹ is caused by the symmetrical deformation mode of the C–CH₃ group [8]. The absorption at 1330 cm⁻¹ can be attributed to the vibrations of the oxazole heterocycles [3, 6, 7].

The anilide (4) is soluble in sodium hydroxide solution and gives a green colour with ferric chloride solution. The IR spectrum of 4 reveals beside the normal bands for α- and β-hydrogen atoms of the furan ring and the C=C stretching modes of the benzene ring, the amide I band at 1645 cm⁻¹ and the amide II band at 1553 cm⁻¹. An amide III band occurs at 1280 cm⁻¹. A broad band appears in the 3110–3205 cm⁻¹ region probably arising from a chelated OH group.

Cyclization of the oxime (2a) with acetic anhydride, gave rise to 4-methoxy-3-methylfuro-
[3,2-f]benzisoxazole (5a). This reaction recalls the observation that cyclization of khellinone oxime (2b) with acetic anhydride furnishes the corresponding benzisoxazole (5b) [9]. Under the same experimental conditions, on the other hand, cyclization of the oxime of visnaginone methyl ether (2c) led only, to the formation of the respective acetyl derivative (6).

\[
\text{OCH}_3 \text{N.O.COCH}_3 \text{OCH}_3 \quad \text{|| C-CH}_3
\]

\[
5a: R = H \\
5b: R = O\text{CH}_3
\]

Structure of the benzisoxazole (5b), is now further confirmed by the study of its NMR spectrum. Its H NMR spectrum (CDCl₃) showed the following assignments: two doublets at 7.65 and 7.05 ppm \(J_{5,6} = 1.4\) c/s (for the furan ring protons), the singlets at 4.30 and at 4.20 ppm (two OCH\(_3\) at C-4 and C-8) and a singlet at 2.65 ppm (CH\(_3\) group at C-3).

The McConnell equation gives a ratio of distance = 0.95 (angle factor neglected), if the methoxyl groups are freely rotating, this is in good agreement with the isoxazolic structure. (For an oxazolic structure the shift ratio would lie around 3-4 with the same condition for the methoxyl groups to rotate freely). The \(^{13}\)C NMR spectrum of 5b, proved the isoxazole structure exclusively. (154 ppm for the isoxazolic C whilst it would be 164 ppm for an oxazolic one) [10].

Utilization of visnaginone (1a) and khellinone (1b) for the synthesis of new furoflavone derivatives was also undertaken. Compounds 1a and 1b condense with benzaldehyde in presence of alkali to give the respective chalcones (7a) and (7b).

When 7a was treated with pyridine hydrochloride at 100–120 °C for 1 h a mixture of about 30% of 4,6-dihydroxy-5-cinnamoylbenzofuran (7c) and 70% of 2-phenyl-5-hydroxy-4H-furo[3,2-g][1]benzopyran-4-one (8a). Methylation of 8a with dimethyl sulphate in acetone in presence of potassium iodide and anhydrous potassium carbonate yielded the already known 2-phenyl-5,9-dimethylxy-4H-furo[3,2-g][1]benzopyran-4-one (8e) (m. p. and mixed m. p. with an authentic specimen prepared by Stener's method [12] gave no depression).

It is of interest to note that whereas Brule and Mentzer [13] have obtained a partially demethylated flavanone derivative by cyclization of the chalcone using pyridine hydrochloride at 155 °C or completely demethylated flavanone by heating at 180 °C, in the present investigation the flavone 8 was obtained directly as confirmed by the presence of a singlet at 6.60 ppm characteristic for the vinyl proton at C₃ in the NMR spectrum of 8a.

When either visnaginone (1a) or khellinone (1b) was treated with pyridine hydrochloride under the same experimental conditions, demethylation of the methoxyl group at C₄ took place leading to the formation of 4,6-dihydroxy- (9a) or 4,6-dihydroxy-7-methoxy-5-benzofuranyl methyl ketone (9b) [11]. When the latter compound was treated with benzaldehyde in the presence of alcoholic sodium hydroxide solution 4,6-dihydroxy-5-cinnamoyl-7-methoxybenzofuran (7d) was produced. Cyclization of 7d was effected using pyridine hydrochloride to form 8b in good yield.

\[
9a: R = H \\
9b: R = \text{OCH}_3
\]
Experimental

Melting points are not corrected. The infrared spectra were carried out in potassium bromide on a Carl Zeiss Infrared spectrophotometer, model “UR 10”. The NMR spectra were carried out in CDCl₃ on a Hitachi Perkin-Elmer and an XL 100.

4-Methoxy-6-hydroxy-5-benzofuranyl methyl ketone oxime (2a)

A mixture of visnaginone (1a) (0.5 g), hydroxylamine hydrochloride (0.5 g) in ethanol (5 ml) and pyridine (0.5 ml) is refluxed for 1 h. After evaporating the volatile materials, water is added (5 ml) while stirring. The solid that separated after cooling is filtered, washed with water and dried. Crystallize from benzene as white needles m.p. 145 °C (75%).

C₁₁H₁₁NO₄
Calcd C 61.80 H 4.72 N 6.01,
Found C 62.13 H 4.84 N 6.34.

4,7-Dimethoxy-6-hydroxy-5-benzofuranyl methyl ketone oxime (2b)

It is obtained as above in 75% yield as colourless crystals from benzene m.p. 145 °C (it proved to be identical with the oxime prepared by Musante [9]).

C₁₂H₁₂NO₄
Calcd C 61.28 H 5.53 N 5.96,
Found C 61.52 H 5.72 N 6.13.

4,6-Dimethoxy-5-benzofuranyl methyl ketone oxime (2c)

Similarly 2c is obtained as white crystals from benzene m.p. 145 °C in 75% yield.

C₁₂H₁₂NO₄
Calcd C 61.28 H 5.53 N 5.96,
Found C 61.52 H 5.72 N 6.13.

4-Methoxy-2-methylfuro[3,2-f]benzoxazole (3a)

The oxime (2a) (2 g) and freshly prepared pyridine hydrochloride (4) is heated for 20 min at about 100 °C. Leave to cool then pour on water and add dilute hydrochloric acid till pH 1. The precipitate is washed well with sodium hydroxide solution (2%) (20 ml) then with water. Crystallize from petroleum ether (b.p. 60–80 °C) as colourless crystals m.p. 90 °C (52%). It gives a negative ferric chloride test.

C₁₁H₉NO₃
Calcd C 65.00 H 4.43 N 6.59,
Found C 64.64 H 4.39 N 7.24.

When the oxime (2c) (2 g) is treated with pyridine hydrochloride as in the case of 2a, 3a is obtained in 49% (m.p. and mixed m.p.). 3a is also obtained in ca. 55% yield by refluxing a mixture of 2a (4 g) in glacial acetic acid (16 ml) saturated with dry hydrogen chloride gas, for 1 h. Leave to cool, then dilute with cold water (200 ml). Filter the solid so obtained and wash with sodium hydroxide solution (2%), then with water to give 3a (m.p. and mixed m.p.).

The alkaline filtrate was treated with concentrated hydrochloric acid till pH 5, extracted with ether, washed with water, dried over anhydrous sodium sulphate then evaporated to give a solid. Crystallize from ethanol as pale yellowish crystals of 4, m.p. 152 °C; yield is ca. 12%. It gives a green colour with aqueous ferric chloride solution.

C₁₂H₁₂NO₄
Calcd C 59.73 H 4.98 N 6.34,
Found C 59.67 H 5.14 N 5.99.

4,8-Dimethoxy-2-methylfuro[3,2-f]benzoxazole (3b)

Treatment of 2b (2 g) with pyridine hydrochloride as in the case of 3a yielded colourless needles from petroleum ether (b.p. 60–80 °C), m.p. 135 °C; yield is ca. 47%. It gives no colour with ferric chloride solution.

C₁₂H₁₂NO₄
Calcd C 61.80 H 4.72 N 6.01,
Found C 61.89 H 5.01 N 6.31.

3b is also obtained in ca. 52% yield by refluxing a mixture of 2b (4 g) in glacial acetic acid (16 ml) saturated with dry hydrogen chloride gas for 1 h. The reaction mixture is worked up to give 3b only (m.p. and mixed m.p.).

4-Methoxy-3-methylfuro[3,2-f]-1,2-benzisoxazole (5a)

Acetic anhydride (1 ml) is added while cooling and stirring to the oxime (2a) (0.5 g). After sometime a crystalline solid separates, pour on water, stir well then leave to cool. Filter the solid so obtained, wash with water and crystallize from ethanol as colourless crystals, m.p. 105 °C, mixed m.p. with 3a gave a depression. It gives no colour with ferric chloride solution.

C₁₂H₁₃NO₃
Calcd C 65.02 H 4.43 N 6.89,
Found C 65.00 H 4.67 N 6.50.

Treatment of the oxime (2c) with acetic anhydride as mentioned above led to the formation of the acetyl derivative (6). Crystallize from ethanol as colourless crystals, m.p. 90 °C; yield is ca. 59%. Mixed m.p. with 5a gave a depression.

C₁₄H₁₅NO₃
Calcd C 60.65 H 5.45 N 5.05,
Found C 61.02 H 5.64 N 5.39.

4,8-Dimethoxy-3-methylfuro[3,2-f]-1,2-benzisoxazole (5b)

Shake while cooling a mixture of 1 g of 2b with 2 ml of acetic anhydride (the solid dissolves after sometime then crystallization starts). Pour on cold water, filter, wash with water then crystallise from ethanol as colourless crystals, m.p. 148 °C (48%).

C₁₂H₁₂NO₄
Calcd C 61.80 H 4.72 N 6.01,
Found C 62.13 H 4.84 N 6.34.
Cyclization of 4-methoxy-6-hydroxy-5-cinnamoyl-benzofuran (7a)

The chalcone (7a) [14] (3 g) is melted with freshly prepared pyridine hydrochloride (6 g; excess) and the reaction mixture is kept at 100–120 °C for 1 h then left to cool. After pouring onto water (20 ml) and acidification with dilute hydrochloric acid, the precipitated yellow material is collected, m.p. 140 °C; yield is ca. 80%. It was crystallised from petroleum ether (b.p. 40–60 °C) to give 7c as yellow solid, m.p. 151 °C (30%).

\[C_{17}H_{12}O_4\]

Calcd C 72.85 H 4.28, Found C 72.55 H 4.12.

The insoluble part was crystallised from benzene to give 8a as yellowish crystals, m.p. 220 °C (70%).

\[C_{10}H_{10}O_4\]

Calcd C 73.38 H 3.59, Found C 73.25 H 3.62.

Cyclization of 4,7-dimethoxy-6-hydroxy-5-cinnamoyl-benzofuran (7b)

Following the same procedure as above, the reaction of 7b (3 g) with pyridine hydrochloride (6 g) yielded a solid m.p. 145 °C, yield is ca. 75%. Fractional crystallisation from petroleum ether (b.p. 60–80 °C) yielded yellowish brown crystals (56%) of 7d, m.p. 147 °C.

\[C_{18}H_{12}O_5\]

Calcd C 69.68 H 4.52, Found C 69.65 H 4.65.

The residue which did not dissolve was crystallised from benzene as yellow crystals of 8b, m.p. 260 °C.

\[C_{18}H_{12}O_5\]

Calcd C 70.13 H 3.89, Found C 69.87 H 4.15.

Compound 8b exhibits a brownish colour reaction with alcoholic ferric chloride solution.

2-Phenyl-5,9-dimethoxy-4H-furo[3,2-g][1]benzopyran-4-one (8c)

A mixture of 8b (0.5 g), dimethyl sulphate (1.5 g), anhydrous potassium carbonate (3 g) and potassium iodide (0.5 g) in dry acetone (15 ml) was refluxed for 14 h. Filter while hot and evaporate the volatile material in vacuum. The residue is crystallised from methanol to give colourless crystals, m.p. 178 °C (70%) mixed m.p. with an authentic specimen [12] gave no depression.

4,6-Dihydroxy-5-benzofuranyl methyl ketone (9a)

A mixture of 3 g of 1a and 6 g of pyridine hydrochloride was melted and kept at 100 °C for 1 h then worked up as described before to give 9a in 62% yield as buff crystals from benzene, m.p. 220 °C.

\[C_{18}H_{14}O_4\]

Calcd C 62.50 H 4.17, Found C 62.89 H 4.12.

4,6-Dihydroxy-7-methoxy-5-benzofuranyl methyl ketone (9b)

A mixture of 1b (3 g) and pyridine hydrochloride (6 g) is melted together and kept at 100 °C for 1 h then worked up in the usual manner to give yellow crystals of 9b from benzene (yield 65%) (m.p. and mixed m.p. with an authentic specimen [11]).

4,6-Dihydroxy-7-methoxy-5-cinnamoyl benzofuran (7d)

A mixture of compound 9b (1 g) and benzaldehyde (0.8 g) is added under good stirring to alcoholic sodium hydroxide solution (5 ml, 10%) then left overnight at room temperature. After acidification with hydrochloric acid, the precipitated material was collected, washed with water then dried. Crystallization from light petroleum (b.p. 60–80 °C) yielded compound 7d as yellowish-brown crystals (60%), m.p. 147 °C.

\[C_{18}H_{14}O_5\]

Calcd C 69.68 H 4.52, Found C 69.60 H 4.65.

Compound 7d gives a brown colour with alcoholic ferric chloride solution.

Preparation of 2-phenyl-5-hydroxy-9-methoxy-4H-furo[3,2-g][1]benzopyran-4-one (8b)

A mixture of 0.7 g of 7d and 3 g of pyridine hydrochloride was melted in the usual manner. The reaction mixture was worked up to yield 52% of 8b as yellow crystals, m.p. 260 °C; mixed m.p. with 8b prepared above gave no depression.

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