[J. Indian Chem. Soc., Vol. 49, No. 6, 1972]

Studies on the Halogenation of Some Flavanones

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Received 25 *January* 1972

2-(α-Naphthyl)chromanone was synthesised and iodinated and brominated and the structures of the products determined by their hydrolysis to the known iodoacetophenone and bromobenzoic acid derivatives.

7-Hydroxy-4′-methoxyflavanone has also been brominated and the structures of the bromo derivatives established by converting them to the corresponding flavones or by hydrolysis to known bromosalicylic acid derivatives.

It appears from the literature that no work in the synthesis of 2-(α-naphthyl)chromanone and its halogenation has been done. It was therefore, thought of interest to study the iodination and bromination of 2-(α-naphthyl)chromanone.

O-Hydroxyacetophenone and α-naphthaldehyde in the presence of ethanolic potassium hydroxide gave an alkali insoluble product, which neither gave colouration with alcoholic ferric chloride solution, nor gave Wilson test[1]. Therefore, 2-(α-naphthyl)chromanone structure was assigned to it.

2-(α-naphthyl)chromanone could not be iodinated with theoretical amounts of iodine and iodic acid, however, with excess of iodinating agents (eight moles), it gave a diiododerivative, which on ethanolic potassium hydroxide hydrolysis gave the known 3,5-diiodo-2-hydroxyacetophenone[2]. 6,8-Diiodo-2-(α-naphthyl)chromanone structure was therefore, assigned to the above product. The same diiododerivative could also be obtained by condensing 3,5-diiodo-2-hydroxyacetophenone[2] with α-naphthaldehyde in the presence of ethanolic potassium hydroxide.

With one or three moles of bromine in acetic acid 2-(α-naphthyl)chromanone yielded a tribromoderivative, which on alkaline hydrolysis gave the known 3,5-dibromo-2-hydroxybenzoic acid[3]. The tribromoderivative when refluxed with acetic acid and potassium acetate yielded 6,8-dibromo-2-(α-naphthyl)chromone, which on alkaline hydrolysis gave the known 3,5-dibromo-2-hydroxybenzoic acid[3]. 3,6,8-Tribromo-2-(α-naphthyl)chromanone structure was therefore, assigned to the above tribromoderivative.

Jagwani and Sethna[4] have studied the iodination of 7-hydroxy-4′-methoxyflavanone. The same has now been brominated.

7-Hydroxy-4′-methoxyflavanone on bromination with one mole of bromine in acetic acid gave a mixture of mono- and dibromoderivative, which was separated by column chromatography over alumina and elution with benzene and ethylacetate mixture (95 : 5). The monobromoderivative on heating with acetic acid and potassium acetate gave the

original monobromoderivative. It did not provide a coumarone derivative[5] when treated with excess of alkali and ethyl alcohol. Therefore, 6-bromo-7-hydroxy-4′-methoxyflavanone structure was assigned to the monobromoderivative. With two moles of bromine in acetic acid it gave a dibromoderivative, the methyl ether of which on alkaline hydrolysis provided the known 5-bromo-4-methoxysalicylic acid[6]. The above dibromoderivative on heating with acetic acid and potassium acetate gave 6-bromo-7-hydroxy-4′-methoxyflavone, the methyl ether of which on ethanolic potassium hydroxide hydrolysis gave the known 5-bromo-4-methoxysalicylic acid[6]. The same dibromoflavanone was also obtained by further bromination of 6-bromo-7-hydroxy-4′-methoxyflavanone. Therefore, 3,6-dibromo-7-hydroxy-4′-methoxyflavanone structure was assigned to the above dibromoderivative. With three moles of bromine in acetic acid it gave tribromoderivative. Its methyl ether on ethanolic potassium hydroxide hydrolysis gave a dibromo acid, which gave violet colouration with alcoholic ferric chloride solution. 3,5-Dibromo-4-methoxysalicylic acid structure was therefore, assigned to the above dibromo acid. The above tribromoflavanone derivative on heating with acetic acid and potassium acetate gave 6,8-dibromo-7-hydroxy-4′-methoxyflavone, m.p. 275°. Nadkarni and Wheeler[7] have prepared 6,8-dibromo-7-hydroxy-4′-methoxyflavone from the corresponding tetrabromochalcone and reported m.p. 194°. The above flavone derivative on methylation gave 7,4′-dimethoxyflavone derivative, which could also be obtained by methylating 3,6,8-tribromo-7-hydroxy-4′-methoxyflavanone with dimethyl sulphate and anhydrous potassium carbonate in acetone. The above tribromoflavanone derivative was also obtained by further bromination of 6-bromo-7-hydroxy-4′-methoxy-, and 3,6-dibromo-7-hydroxy-4′-methoxyflavanone as described above. It was also obtained by further bromination of 6,8-dibromo-7-hydroxy-4′-methoxyflavanone, obtained by condensing 3,5-dibromoresacetophenone[6] with anisaldehyde in the presence of ethanolic potassium hydroxide. Therefore, 3,6,8-tribromo-7-hydroxy-4′-methoxyflavanone structure was assigned to the above tribromoderivative. The purity of all the compounds was checked by T.L.C.

EXPERIMENTAL*

2-(α-Naphthyl)chromanone : α-Naphthaldehyde (5 g.) and *o*-hydroxyacetophenone (5 g.) were dissolved in ethyl alcohol (45 ml.) and potassium hydroxide solution (100%, 10 ml) added to it. The reaction mixture was kept in a bulb oven at 60° for 12 hrs. when a yellow crystalline product separated. It was crystallised from glacial acetic acid in yellow needles, m.p. 125°. Yield 5 g. It did not give any colouration with alcoholic ferric chloride and with a mixture of a solution of citric acid in dry acetone and boric acid in dry acetone (Wilson test[1]). The compound gave a single spot on T.L.C. (R_f 0·6) using benzene as developer. (Found : C, 83·58; H, 4·89; $C_{19}H_{14}O_2$ requires C, 83·21; H, 5·10%).

6,8-Diiodo-2-(α-naphthyl)chromanone : 2-(α-Naphthyl)chromanone (0·342 g.) and iodine (1 g.) were dissolved in alcohol (50 ml.) and heated to about 60° and iodic acid (0·2 g.) in water added with stirring during 1½ hrs. The separated product was crystallised from benzene in orange yellow needles, m.p. 171°. Yield 0·3 g. The same product was also

* All the m.p.s. are uncorrected.

prepared by condensing 3,5-diiodoacetophenone[2] (1 g.) and α-naphthaldehyde (1 g.) in the presence of alcoholic potassium hydroxide as above. (Found : I, 47·96. $C_{19}H_{12}O_2I_2$ requires I, 48·28%).

The above chromanone derivative (1·0 g.) was refluxed with alcoholic potassium hydroxide (20%, 40 ml.) for 2½ hrs. on a steam bath. The reaction mixture was poured into ice cold water and filtered. The filtrate on acidification with concentrated hydrochloric acid gave a product, which was extracted with ether. The ether extract was treated first with sodium bicarbonate solution and then with sodium hydroxide solution. Sodium hydroxide extract on acidification gave 3,5-diiodo-2-hydroxyacetophenone[2]. It was crystallised from acetic acid (50%), in colourless needles, m.p. and mixed m.p. with an authentic specimen was 127°.

3,6,8-*Tribromo*-2-(*α-naphthyl*)*chromanone* : 2-(α-Naphthyl)chromanone (0·276 g.) was dissolved in glacial acetic acid (15 ml.) and bromine in acetic acid (10%, 25 ml.) added to it and the reaction mixture kept overnight. The separated product was crystallised from *o*-xylol in yellow needles, m.p. 212°. Yield 0·25 g. (Found : Br, 46·90. $C_{19}H_{11}O_2Br_3$ requires Br, 46·97%).

The above chromanone derivative was refluxed with alcoholic potassium hydroxide (10%, 40 ml.) on a steam bath for 4½ hrs. On working up the reaction mixture as usual, it gave 3,5-dibromo-2-hydroxybenzoic acid[3]. It was crystallised from alcohol (50%), m.p. and mixed m.p. with an authentic specimen was 225°.

6,8-*Dibromo*-2-(*α-naphthyl*)*chromone* : The above tribromochromanone derivative (1 g.) was dissolved in acetic acid (15 ml.) and potassium acetate (1 g.) added to it. The reaction mixture was refluxed on a wire gauze for 3½ hrs. The reaction mixture on cooling gave a product, which crystallised from toluene in yellow needles (0·5 g.) m.p. 207°. (Found : C, 52·81; H, 2·77; Br, 37·08. $C_{19}H_{10}O_2Br_2$ requires C, 53·02; H, 2·32; Br, 37·21%).

The above chromone derivative (1 g.) on hydrolysis with potassium hydroxide (10%, 40 ml.) as described above, gave a product, which crystallised from (50%) alcohol, m.p. and mixed m.p. with an authentic specimen of 3,5-dibromo-2-hydroxy benzoic acid was 225°.

6-*Bromo*-7-*hydroxy*-4′-*methoxyflavanone* : Bromine in acetic acid (10%, 6·4 ml.) was added to a mixture of fused sodium acetate (0·5 g.) and 7-hydroxy-4′-methoxyflavanone (1·08 g.) in hot and the reaction mixture was left overnight and then poured in ice cold water. It gave a mixture of mono- and dibromoderivative. The monobromoderivative separated from dibromoderivative by column chromatography over alumina, elution with benzene and ethylacetae mixture (95 : 5), m.p. 210°. Yield 0·2 g. (Found : Br, 23·23. $C_{16}H_{13}O_4Br$ requires Br, 22·93%). The monobromoderivative (1 g.) on refluxing with potassium acetate (1 g.) in acetic acid (15 ml.) gave the original product. When treated with excess of ethanolic alkali, it did not provide coumarone derivative but gave the original product, m.p. 210°.

3,6-*Dibromo*-7-*hydroxy*-4′-*methoxyflavanone* : Bromine in acetic acid (10%, 12·8 ml.) was added to a mixture of fused sodium acetate (0·5 g.) and 7-hydroxy-4′-methoxyflavanone

(1·08 g.) in acetic acid (15 ml.) and left overnight. The reaction mixture was poured in ice cold water. The separated product crystallised fsom glacial acetic acid, m.p. 189°. The same dibromoderivative was also prepared by further bromination of 6-bromoflavanone derivative (0·349 g.) and bromine in acetic acid (10%, 1·6 ml.) as described above. (Found: Br, 37·64. $C_{16}H_{12}O_3Br_2$ requires Br, 37·40%).

3,6-*Dibromo*-7-4′-*dimethoxyflavanone* : Above flavanone derivative (1 g.), dimethyl sulphate (1·2 g.) and anhydrous potassium carbonate (3 g.) in dry acetone (25 ml.) were refluxed on a steam bath for 8 hrs. After removing acetone it was diluted with ice cold water, when the product separated. It crystallised from acetic acid, m.p. 238°. Yield 0·7 g. (Found : C, 46·44; H, 3·55; Br, 36·61. $C_{17}H_{14}O_4Br_2$ requires C, 46·15; H, 3·16; Br, 36·20%).

The above dimethoxyflavanone derivative (1 g.), on hydrolysis with alcoholic potassium hydroxide (10%, 40 ml.) gave a product, which crystallised from acetic acid (50%), m.p. and mixed m.p. with an authentic specimen of 5-bromo 4-methoxy salicylic acid[6] was 250°.

6-*Bromo*-7-*hydroxy*-4′-*methoxyflavone* : Potassium acetate (1 g.) was added to a solution of 3,6-dibromo-7-hydroxy-4′-methoxyflavanone (1 g.) in acetic acid (15 ml.). The reaction mixture was refluxed on a wire gauze for 3½ hrs. On cooling the product was obtained, which crystallised from dioxan, m.p. 315°. Yield 0·5 g. (Found : C, 55·22; H, 3·44; Br, 23·30. $C_{16}H_{11}O_4Br$ requires C, 55·34; H, 3·17; Br, 23·05%).

6-*Bromo*-7-4′-*dimethoxyflavone* : The above flavone derivative (1 g.) dimethyl sulphate (1·2 g.), dry acetone (25 ml.) and anhydrous potassium carbonate (3 g.) were refluxed on a steam bath for 8 hrs. On working up as usual, it gave a product, which crystallised from acetic acid (50%) in pale yellow needles (0·6 g.), m.p. 207°. (Found : C, 56·44; H, 3·44; Br, 22·41. $C_{17}H_{13}O_4Br$ requires C, 56·50; H, 3·60; Br, 22·16%).

The above dimethoxyflavone derivative (1 g.), on hydrolysis with alcoholic potassium hydroxide (10%, 40 ml.) as described above gave a product, which crystallised from acetic acid (50%), m.p. and mixed m.p. with an authentic specimen of 5-bromo-4-methoxy salicylic acid[6] was 250°.

3,6,8-*Tribromo*-7-*hydroxy*-4′-*methoxyflavanone* : Bromine in acetic acid (10%, 19·4 ml.) was added to 7-hydroxy-4′-methoxyflavanone (1·08 g.) and in acetic acid (15 ml.) and the reaction mixture left overnight. The separated product crystallised from acetic acid in pale yellow needles (1 g.), m.p. 162°. The same compound was also prepared by further bromination of 6-bromo-7-hydroxy-4′-methoxy- (0·349 g.) and 3,6-dibromo-7-hydroxy-4′-methoxyflavanone (0·428 g.) with bromine in acetic acid (10%, 3·2 ml.) and (10%, 1·6 ml.) respectively as described above. It was also prepared by further bromination of 6,8-dibromo-7-hydroxy-4′-methoxyflavanone (0·428 g.) as described below, with bromine in acetic acid (10%, 1·6 ml.). (Found : Br, 47·08. $C_{16}H_{11}O_4Br_3$ requires Br, 47·34%).

6,8-*Dibromo*-7-*hydroxy*-4′-*methoxyflavanone* : 3,5-Dibromoresacetophenone[6] (5 g.) and anisaldehyde (5 g.) were dissolved in ethyl alcohol (50 ml.) and potassium hydroxide solution (100%, 10 ml.) added to it. The reaction mixture was kept in a bulb oven at 60° for 12

to 15 hrs. The reaction mixture on dilution and acidification gave a product, which crystallised from glacial acetic acid as yellow needles (6 g.), m.p. 184°. (Found : C, 45·26; H, 3·22; Br, 37·71. $C_{16}H_{12}O_4Br_2$ requires C, 44·86; H. 2·80; Br, 37·39%).

6,8-*Dibromo*-7,4′-*dimethoxyflavone* : It was prepared by methylating 3,6,8-tribromo-7-hydroxy-4′-methoxyflavanone (1 g.) with dimethyl sulphate (1·2 g.) and anhydrous potassium carbonate (3 g.) in acetone (25 ml.) as described above. It crystallised from glacial acetic acid in pale yellow needles (0·7 g.), m.p. 249°. (Found : C, 46·01; H, 3·28; Br, 36·53. $C_{17}H_{12}O_4Br_2$ requires C, 46·36; H, 2·94; Br, 36·36%).

3,5-*Dibromo*-4-*methoxysalicylic acid* : Above dimethoxyflavone derivative (1 g.) on hydrolysis with alcoholic potassium hydroxide (10%, 40 ml.) for 4 hrs. gave a product, which crystallised from acetic acid (25%). m.p. 167°. It gave a violet colouration with alcoholic ferric chloride solution. (Found : C, 29·21; H, 1·98; Br, 48·73. $C_8H_6O_4Br_2$ requires C. 29·46; H, 1·84; Br, 49·07%).

6,8-*Dibromo*-7-*hydroxy*-4′-*methoxyflavone* : 3,6,8-Tribromo-7-hydroxy-4′-methoxyflavanone (1 g.) was dissolved in acetic acid (15 ml.) and potassium acetate (1 g.) was added to it. The reaction mixture was refluxed on a wire gauze for $3\frac{1}{2}$ hrs. On cooling it gave a product, which crystallised from dioxan, m.p. 275°. Yield 0·5 g. (Found : C, 45·23; H, 2·54; Br, 37·70. $C_{16}H_{10}O_4Br_2$ requires C, 45·08; H, 2·34; Br, 37·56%).

The above flavone derivative (1 g.) when methylated with dimethyl sulphate (1·2 g.) and anhydrous potassium carbonate (3 g.), in dry acetone (25 ml.) as before, gave 6,8-dibromo-7,4′-d methoxyflavone, m.p. and mixed m.p. with the product described above was 249°.

The purity of all the compounds was checked by thin layer chromatography on silica gel, using benzene and ethylacetate mixture (95 : 5) as the developer solvents. The spots on T.L.C. plates could be located clearly by virtue of their yellow colour. Some times, however, the exposure of the T.L.C. plates to iodine vapours was found to be advantageous.

Thanks are due to Principal G. R. Mhaisekar for encouraging the research activities in the department. Thanks are also due to Prof. S. Sethna, M. S. University of Baroda for his keen interest in the work and to Dr. S. S. Lele for carrying out micro analysis.

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