SYNTHETIC EXPERIMENTS IN THE BENZOPYRONE SERIES

Part XI. Conversion of Carthamidin and Isocarthamidin into Herbacetin and Tangeretin

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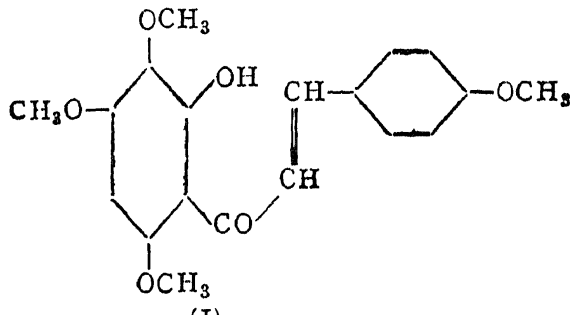
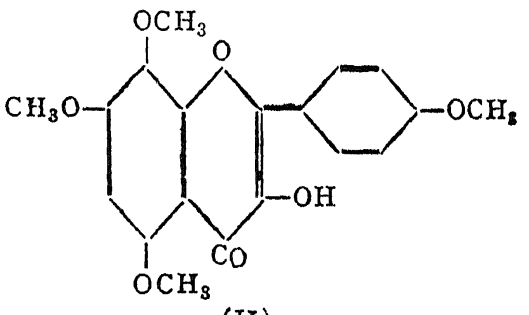
THE synthesis of carthamidin and isocarthamidin has been recently reported by us.[1] A convenient method of providing confirmation of their constitution would be to convert them into the related flavonols, herbacetin and tangeretin. Earlier, Bargellini[2] reported the oxidation of 2-hydroxy-3:4:6:4′-tetramethoxy chalkone (I) (chalkone of carthamidin tetramethyl ether) by means of alkaline hydrogen peroxide to yield herbacetin tetramethyl ether (II). But more recently Geismann and Fukushima[3] have carefully investigated this reaction and have shown that when the concerned 2-hydroxy chalkone has a methoxyl group in the 6-position it gives rise predominantly to a benzal-coumaranone and only very minor quantities or nil of the corresponding flavonol is obtained. As a typical example could be mentioned the case of 2-hydroxy-4:6:4′-trimethoxy chalkone (III) which was found to produce very little of the corresponding kæmpferol derivative but formed the corresponding 4:6:4′-trimethoxy benzalcoumaranone (IV) in good yields. This reaction has been repeated by us and the result confirmed. Recently the oxidation of 2-hydroxy-3:4:6-trimethoxy chalkone to 4:6:7-trimethoxy benzalcoumaranone was reported by Balakrishna,



(I)



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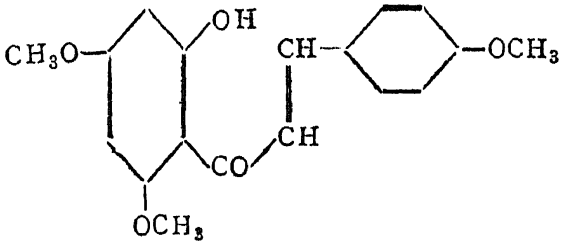
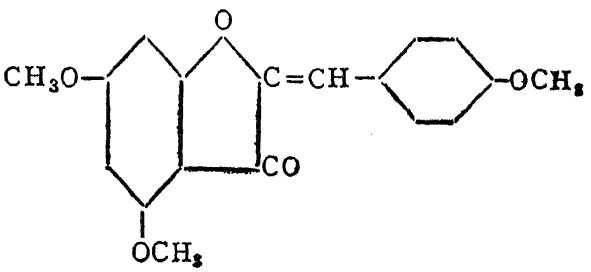


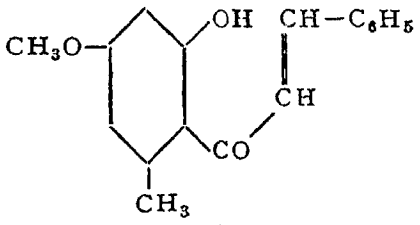
(III)



(IV)

Seshadri and Viswanath.[4] A similar change of the isomeric 2-hydroxy-4:5:6-trimethoxy chalkone is reported in this paper.

While discussing the mechanism of this reaction Geismann and Fukushima[3] expressed the opinion that the influence of the 6-methoxyl group is steric in nature. As a relevant example useful for this purpose 2-hydroxy-4-methoxy-6-methyl chalkone (V) having a methyl group instead of methoxyl group in the 6-position has now been prepared from orcacetophenone monomethyl ether and benzaldehyde and subjected to this oxidation. The product is insoluble in alkali and gives no colour reaction with ferric chloride showing that it is not a flavonol derivative. On the other hand its composition and reactions agree with the requirements for the benzalcoumaranone structure (VI), thus indicating that even a methyl group in the 6-position has the same effect as a methoxyl group. In this connection should be mentioned the interesting results recorded by Venkataraman and co-workers[5] that when chalkones with a free hydroxyl in the 4′-position are employed, the characteristic effect of a 6-methoxyl is not found and a flavonol is produced in the oxidation. The typical example is the formation of quercetin trimethyl ether (VII) from the dihydroxy chalkone (VIII).



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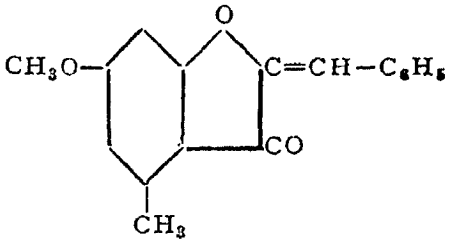

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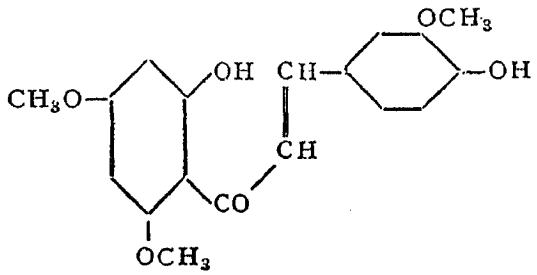

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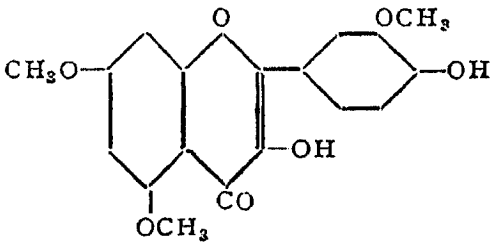
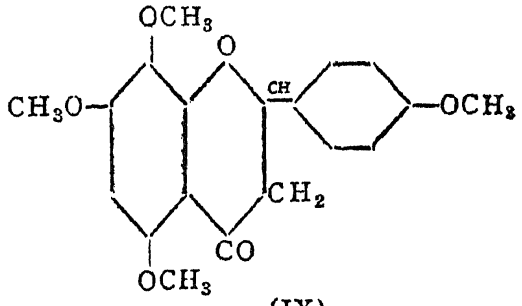


(VII)

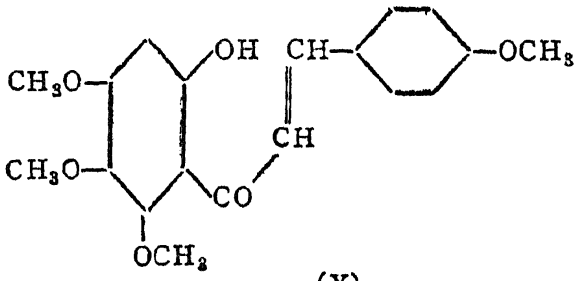
In view of the existence of possible ambiguity in Bargellini's conversion of the tetramethoxy chalkone (I) into herbacetin derivative the experiment has now been repeated. In agreement with the observation of Geismann, *et al.*, the product is found to be a benzalcoumaranone and not a flavonol derivative. However, by adopting the amyl nitrite method of Kostanecki[6] with the simplification employed by Row and Seshadri,[7] carthamidin tetramethyl ether (IX) readily yields herbacetin tetramethyl ether (II) with a free hydroxyl in the 3-position. This is quite different from the hydrogen

peroxide oxidation product and is a useful reference compound for the study of 3-glycosides of herbacetin; on methylation it yields herbacetin pentamethyl ether.

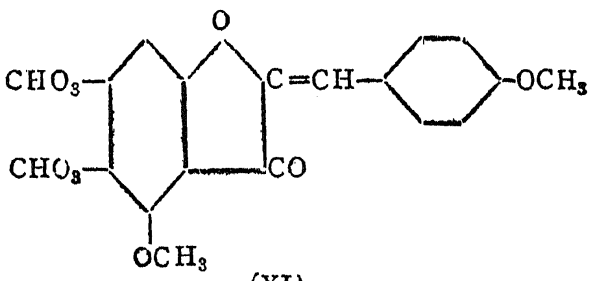
Closely analogous results have been obtained with isocarthamidin derivatives also. The chalkone tetramethyl ether[1] (X) yields the corresponding benzal coumaranone (XI) by treatment with alkaline hydrogen peroxide, whereas by treatment with amyl nitrite of the flavanone (XII) the tetramethyl ether of nor-tangeretin (XIII) is produced. This is a useful reference compound for the study of nor-tangeretin-3-glycosides and on methylation yields tangeretin.



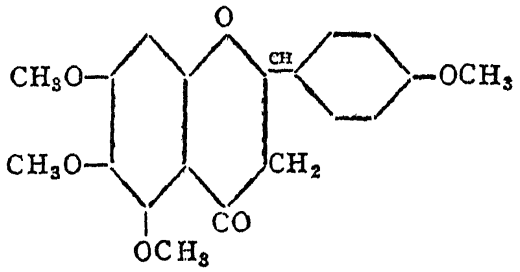
(IX) ⟶ (II)



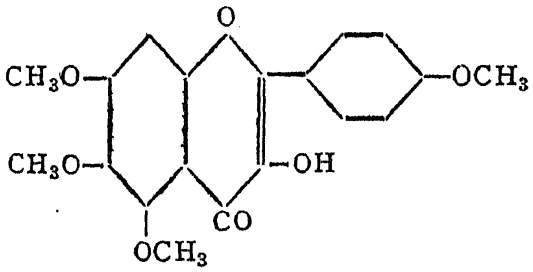
(X)



(XI)



(XII)



(XIII)

Experimental

1. *Oxidation of 2-hydroxy-4: 5: 6-trimethoxy chalkone with hydrogen peroxide*

An ice-cooled solution of 2-hydroxy-4: 5: 6-trimethoxy chalkone[1] (0·5 g.) in alcohol (5 c.c.) was treated with aqueous sodium hydroxide (5 c.c., 2 N.). To this was added an aqueous solution of hydrogen peroxide (2 c.c., 6%) in small quantities with vigorous shaking and the cooling continued for two hours. Turbidity developed slowly in the course of one hour and at the end of two hours a pale yellow crystalline powder separated. The mixture was diluted with water (10 c.c.) and extracted with ether. On

evaporating the ether solution a sticky yellow solid was obtained. It crystallised from alcohol in the form of yellow tiny prisms melting at 142–43°. It was insoluble in aqueous alkali and gave no colour with ferric chloride in alcoholic solution. With concentrated sulphuric acid it gave a deep red colour. It thus had all the properties required for 4: 5: 6-trimethoxy benzal-coumaranone. Yield 0·25 g. (Found: C, 68·8; H, 5·4; $C_{18}H_{16}O_5$ requires C, 69·1; H, 5·1%.) Acidification of the alkaline solution gave no product.

2. *2-Hydroxy-4-methoxy-6-methyl chalkone (V): Preparation*

A mixture of 4-O-methyl-orcacetophenone (1 g.) and benzaldehyde (3 c.c.) was dissolved in alcohol (20 c.c.) and sodium hydroxide solution (3 g. in 3 c.c. water) added with cooling under the tap. The flask was corked air tight and kept at room temperature for 48 hours. It was then diluted with water (50 c.c.) and extracted with ether to remove excess of benzaldehyde and acidified with concentrated hydrochloric acid. The chalkone that separated was extracted with ether and the ether solution washed with aqueous sodium bicarbonate. On distilling off ether a yellow sticky solid was obtained. It crystallised from alcohol as yellow prisms melting at 125–27°. It gave a brown colour with ferric chloride in alcohol and dissolved in aqueous sodium hydroxide. Yield 0·7 g. (Found: C, 75·9; H, 6·3; $C_{17}H_{16}O_3$ requires C, 76·1; H, 6·0%.)

3. *Oxidation with hydrogen peroxide*

To a solution of the above chalkone (0·5 g.) in alcohol (10 c.c.) sodium hydroxide (5 c.c., 10%) was added and the solution cooled in ice. Hydrogen peroxide (2·5 c.c., 6%) was slowly added little by little with shaking and the product worked up just as in experiment (1). It crystallised from dilute alcohol in the form of pale yellow tiny prisms melting at 136–38°. It gave a deep red colour with conc. sulphuric acid and was insoluble in aqueous alkali. Its alcoholic solution gave no colour with ferric chloride. Thus its properties agreed with the requirements of 4-methyl-6-methoxy benzal-coumaranone (VI). (Found: C, 76·4; H, 5·6; $C_{17}H_{14}O_3$ requires C, 76·7; H, 5·3%.)

4. *Oxidation of 2-hydroxy-3: 4: 6: 4′-tetramethoxy chalkone (I)*

A solution of the chalkone[2] (1 g.) in alcohol (20 c.c.), sodium hydroxide solution (10 c.c., 10%) and hydrogen peroxide solution (5 c.c., 6%) were employed and the product worked up as described in the above experiments. 4: 6: 7: 4′-Tetramethoxy-benzalcoumaranone crystallised from alcohol in the form of bright yellow rhombohedral prisms melting at 200–01°. Yield 0·5 g. It gave a deep red colour with concentrated sulphuric acid. It was insoluble in aqueous alkali and gave no colour with ferric chloride in

alcoholic solution. (Found: C, 66·7; H, 5·7; $C_{19}H_{18}O_6$ requires C, 66·7; H, 5·3%.)

The aqueous alkaline solution left after the complete removal of the benzal coumaranone was acidified with concentrated hydrochloric acid and extracted with ether. On evaporating the ether solution a small quantity of a colourless solid was obtained. It dissolved completely in aqueous sodium bicarbonate and was identical with anisic acid.

5. *Preparation of* 5: 7: 8: 4′-*tetramethoxy*-3-*hydroxy flavone* (*II*)

5: 7: 8: 4′-Tetramethoxy flavanone[2] (IX), m.p. 152–54° (1 g.), was dissolved in alcohol (40 c.c.) and the solution kept gently boiling over a small flame. Amyl nitrite (3 c.c.) and fuming hydrochloric acid (20 c.c., d. 1·19) were added alternately little by little with continuous stirring. After the addition, the mixture was allowed to stand for two hours with occasional shaking. It was then diluted with water (150 c.c.) and the solid product filtered and washed with water. Yield 0·3 g. A further small quantity was obtained by ether extracting the acid solution. The ether solution was extracted with aqueous sodium hydroxide and the alkaline solution on acidification gave the hydroxy-flavone. Total yield 0·35 g. On crystallisation from alcohol, 3-hydroxy-5: 7: 8: 4′-tetramethoxy flavone was obtained as bright yellow rectangular rods and needles melting at 198–200°. It dissolved readily in aqueous alkali and formed a sparingly soluble sodium salt in concentrated solution. It gave a reddish brown colour with alcoholic ferric chloride. When reduced in alcoholic solution with magnesium and hydrochloric acid an orange red colour was developed. With concentrated sulphuric acid it formed a yellow solution with a green fluorescence. (Found: C, 64·0; H, 4·7; $C_{19}H_{18}O_7$ requires C, 63·7; H, 5·0%.) A mixture of this substance with the product of experiment (4) melted below 160°.

6. *Methylation*

The above 3-hydroxy flavone (0·3 g.) was refluxed in acetone solution with dimethyl sulphate (0·1 c.c.) and anhydrous potassium carbonate (0·5 g.) for 6 hours. It was then filtered and the potassium salts washed with hot acetone. On distilling off acetone a pale yellow solid was obtained. It crystallised from dilute alcohol as colourless rectangular rods and needles melting at 155–56°. It was insoluble in aqueous alkali and gave no colour with ferric chloride in alcohol. It agreed in its properties with herbacetin pentamethyl ether[8] and a mixed melting point with an authentic sample was undepressed.

7. *Ethylation* (*Preparation of* 3-*ethoxy*-5 : 7 : 8 : 4′-*tetramethoxy flavone*)

3-Hydroxy-5 : 7 : 8 : 4′-tetramethoxy flavone (0·2 g.) was dissolved in acetone (20 c.c.), ethyl iodide (0·2 c.c.) and anhydrous potassium carbonate (1 g.) were added and the mixture refluxed for 6 hours. Acetone was then distilled off and the residue treated with water and extracted with ether. On evaporating the ether solution 3-ethoxy 5 : 7 : 8 : 4′-tetramethoxy flavone was obtained as a pale yellow solid. It crystallised from dilute alcohol in the form of almost colourless clusters of needles and melted at 97–98°. It was insoluble in aqueous alkali and gave no colour with ferric chloride in alcoholic solution. When reduced with magnesium and hydrochloric acid its alcoholic solution gave a scarlet red colour. With concentrated sulphuric acid it gave a yellow solution without any fluorescence. (Found: C, 65·3; H, 5·5; $C_{21}H_{22}O_7$ requires C, 65·3; H, 5·7%.)

8. *Oxidation of* 2-*hydroxy*-4 : 5 : 6 : 4′-*tetramethoxy chalkone* (*X*)

This chalkone,[1] on treatment with hydrogen peroxide as described in the above experiments, gave 4 : 5 : 6 : 4′-tetramethoxy benzalcoumaranone (XI) in 50% yield. It crystallised from alcohol in the form of stout yellow rectangular rods melting at 189–90°. Its colour reactions were similar to those already described. (Found: C, 66·3; H, 5·6; $C_{19}H_{18}O_6$ requires C, 66·7; H, 5·3%.) The aqueous solution left after removing the benzalcoumaranone on acidification gave a small quantity of anisic acid.

9. 3-*Hydroxy*-5 : 6 : 7 : 4′-*tetramethoxy flavone* (*XIII*)

To a gently boiling solution of isocarthamidin tetramethyl ether[1] (XII) (1 g.) in alcohol (40 c.c.) were added alternately amyl nitrite (3 c.c.) and concentrated hydrochloric acid (20 c.c., d. 1·19) little by little with stirring. After the addition, the mixture was left for two hours with occasional shaking; a bright yellow solid separated gradually. It was then diluted with water (100 c.c.) and the solid product filtered and washed with water. On working up the aqueous solution as described in a previous experiment some more of the product could be isolated. It was twice crystallised from alcohol when the flavonol was obtained as bright yellow rhombic plates melting at 171–73°. It dissolved in aqueous alkali easily and gave a dark brown colour with ferric chloride in alcohol. With concentrated sulphuric acid it gave a yellow solution with a green fluorescence. Yield 0·35 g. (Found: C, 63·7; H, 5·0; $C_{19}H_{18}O_7$ requires C, 63·7; H, 5·0%.)

10. *Methylation*

The above 3-hydroxy compound (0·2 g.) was methylated with dimethyl sulphate (0·1 c.c.) and anhydrous potassium carbonate (0·5 g.) in dry acetone, by refluxing for 6 hours. The mixture was then filtered and the

potassium salts washed with hot acetone. On distilling off acetone a pale yellow solid was obtained. It crystallised from alcohol in the form of colourless rectangular plates melting at 153–54°. It was insoluble in aqueous alkali and gave no colour with ferric chloride in alcohol. It agreed in its properties with tangeretin[9] and the mixed melting point with a sample of tangeretin was undepressed.

Summary

A convenient method of providing confirmation of the constitution of carthamidin and isocarthamidin is to convert them into herbacetin and tangeretin. The earlier claim of Bargellini to have prepared herbacetin tetramethyl ether by the oxidation of 2-hydroxy-3:4:6:4′-tetramethoxy chalkone with alkaline hydrogen peroxide could not be supported. This reaction yields the corresponding benzalcoumaranone and not flavonol in agreement with the behaviour of analogous and simpler chalkones having a methoxyl group in the 6-position. An example is described where even a methyl group in that position brings about the same result. However by the action of amyl nitrite and hydrochloric acid carthamidin and isocarthamidin tetramethyl ethers yield the corresponding flavonol derivatives.

References

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2. Bargellini .. *Br. Chem. Abs.*, 1940, Aii, 186.
3. Geismann and Fukushima .. *J. A. C. S.*, 1948, 1686.
4. Balakrishna, Seshadri and Viswanath *Proc. Ind. Acad. Sci.*, A, 1949, **30**, 120.
5. Anand, Iyer and Venkataraman .. *Ibid.*, 1949, **29**, 203.
6. Kostanecki and Tambor .. *Ber.*, 1899, **32**, 2260; 1904, **37**, 792.
7. Row and Seshadri .. *Proc. Ind. Acad. Sci.*, A, 1945, **21**, 180; 1946, **23**, 97.
8. Rangaswami and Seshadri .. *Ibid.*, 1939, **9**, 133.
9. Goldsworthy and Robinson .. *J. C. S.*, 1937, 46.
   Row and Seshadri .. *Proc. Ind. Acad. Sci.*, A, 1946, **23**, 23.

Addendum

After this communication had been written up we received the papers of Oliverio,[10] *et al.*, dealing with the hydrogen peroxide oxidation of chalkones I and X and related members. They have considered the products to be flavonols, but have not recorded their ferric reaction or alkali solubility. They seem to be unaware of the work of Geismann and Fukushima and the possibility of the products being benzalcoumaranones. Their preparations are therefore not free from ambiguity and they differ in their properties from ours.

10. *Gazzetta*, 1948, **78**, 363 and 372.