COLOURING MATTER OF TAMBUL SEEDS

Part III. Synthesis of 3: 8: 4′-Trimethyl Ether of Herbacetin and the Constitution of Tambulin

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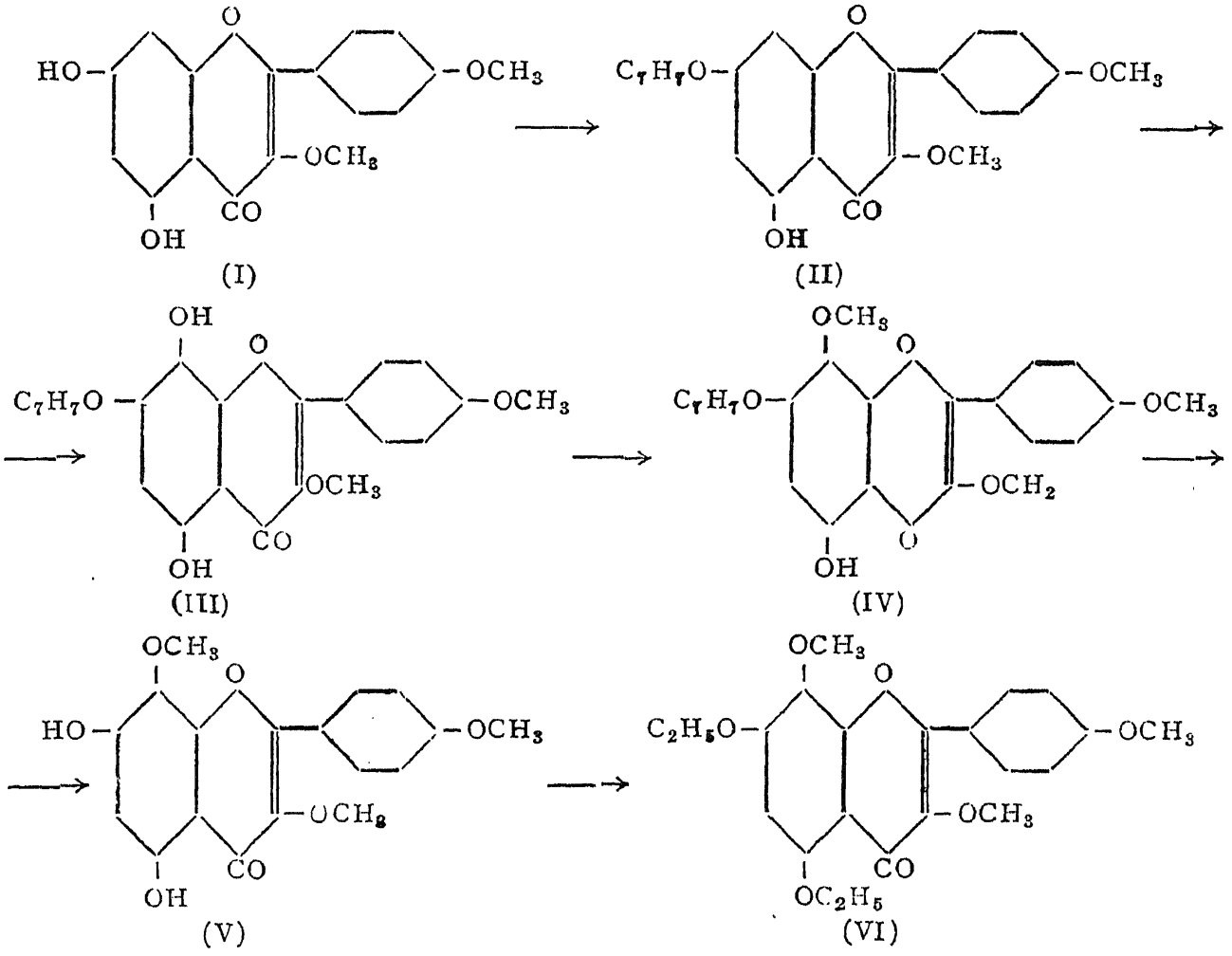
In the earlier publication (Parts I and II)[1] on this subject the isolation of tambuletin and its constitution were discussed. It was established that tambuletin is the 8-methyl-ether of herbacetin and the synthesis of its tri- and tetra-ethyl-ethers was accomplished. The constitution of tambulin, a compound isolated earlier by Bose and Bose[2] from the tambul seeds is examined in this paper.

The above workers showed that tambulin was a trimethyl ether of herbacetin and a methoxyl group was located in the 4′-position since anisic acid could be isolated as one of the products of alkali fission. They considered that another methoxyl was present in the 3-position since the compound was stable to aerial oxidation in dilute alkali. Alkaline *o*-dinitrobenzene and chloropentamine cobaltichloride were not reduced by tambulin thus indicating that it did not have ortho or para dihydroxyl groups and hence the third methoxyl was placed in the 8-position. Thus the constitution of tambulin was suggested to be 3: 8: 4′-trimethyl ether of herbacetin. A substance of this structure has now been synthesised without any difficulty by making use of the recent discovery of facile nuclear oxidation in the 8-position of flavones and flavonols.

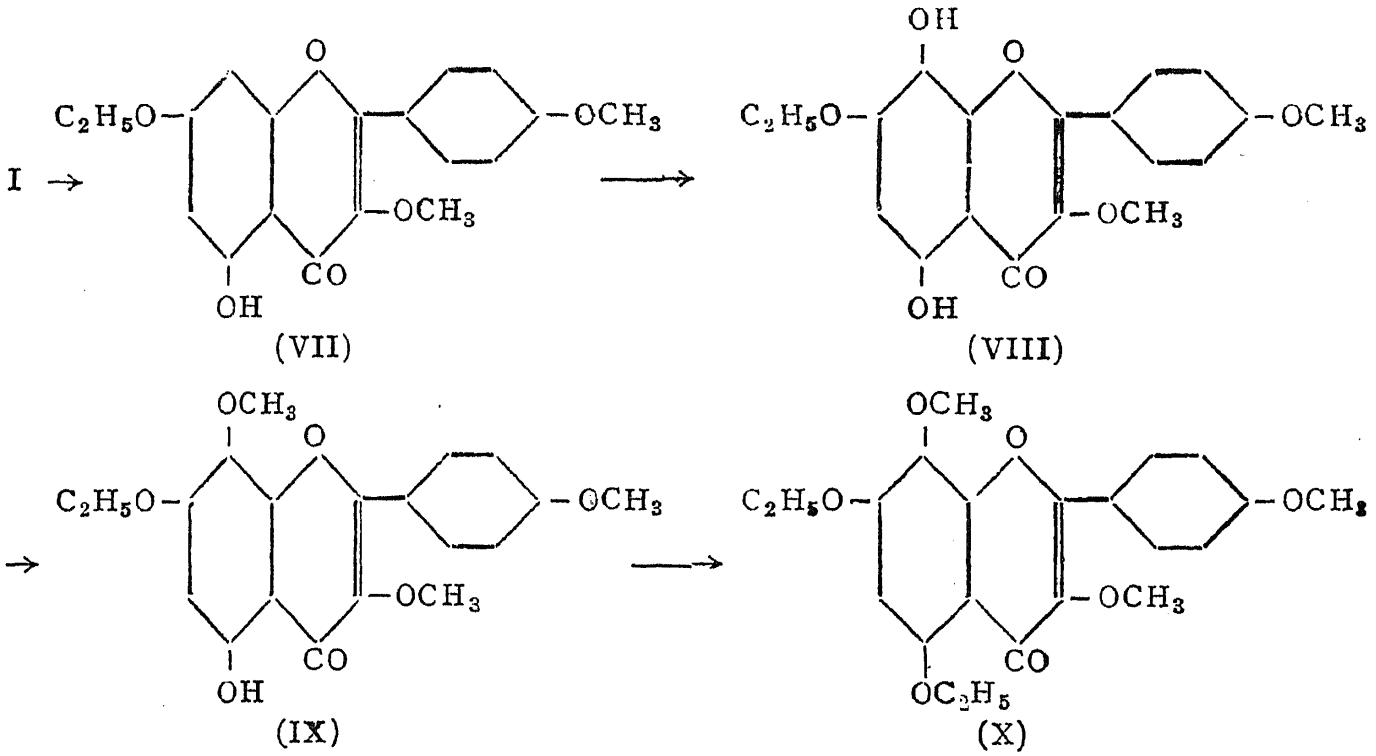
The first stage in the synthesis is 3: 4′-dimethyl-ether of kaempferol (I) which is readily made from ω-methoxy-phloroacetophenone and anisic acid by the Allan-Robinson condensation.[3] It is subjected to partial benzylation when the 7-benzyl-ether (II) is obtained, the resistant 5-hydroxyl being unaffected. The constitution of this compound arises not only from analogy with partial methylation[4] but is also supported by its properties and reactions. It is sparingly soluble in alkali and gives a strong ferric reaction characteristic of a free hydroxyl in the 5-position. Subsequent nuclear oxidation yields the quinol (III) and partial methylation the compound (IV) which again gives reactions characteristic of the free 5-hydroxyl. Similar series of reactions have been recently reported in connection with the synthesis of wogonin.[5] Final debenzylation produces the required trimethyl

ether, 3:8:4′-O-trimethyl herbacetin (V). This crystallises from alcohol in the form of straw yellow rectangular plates and needles and melts at 248–50°. Its acetyl derivative melts at 178–80°. Thus it is different from tambulin which is reported to crystallise from glacial acetic acid as deep yellow plates melting at 205° and yield an acetyl derivative melting at 160–61°. The constitution of tambulin therefore is still undetermined. It may here be remarked that the melting point of 205° should be too low for a 5:7-dihydroxy-compound (V) since even the 7-hydroxy-compound (XI) melts much higher (269–70°). Tambulin is not reported to form a hydrate which may account for a lower melting point. The higher melting point now recorded for the synthetic trimethyl-ether accords with expectations.



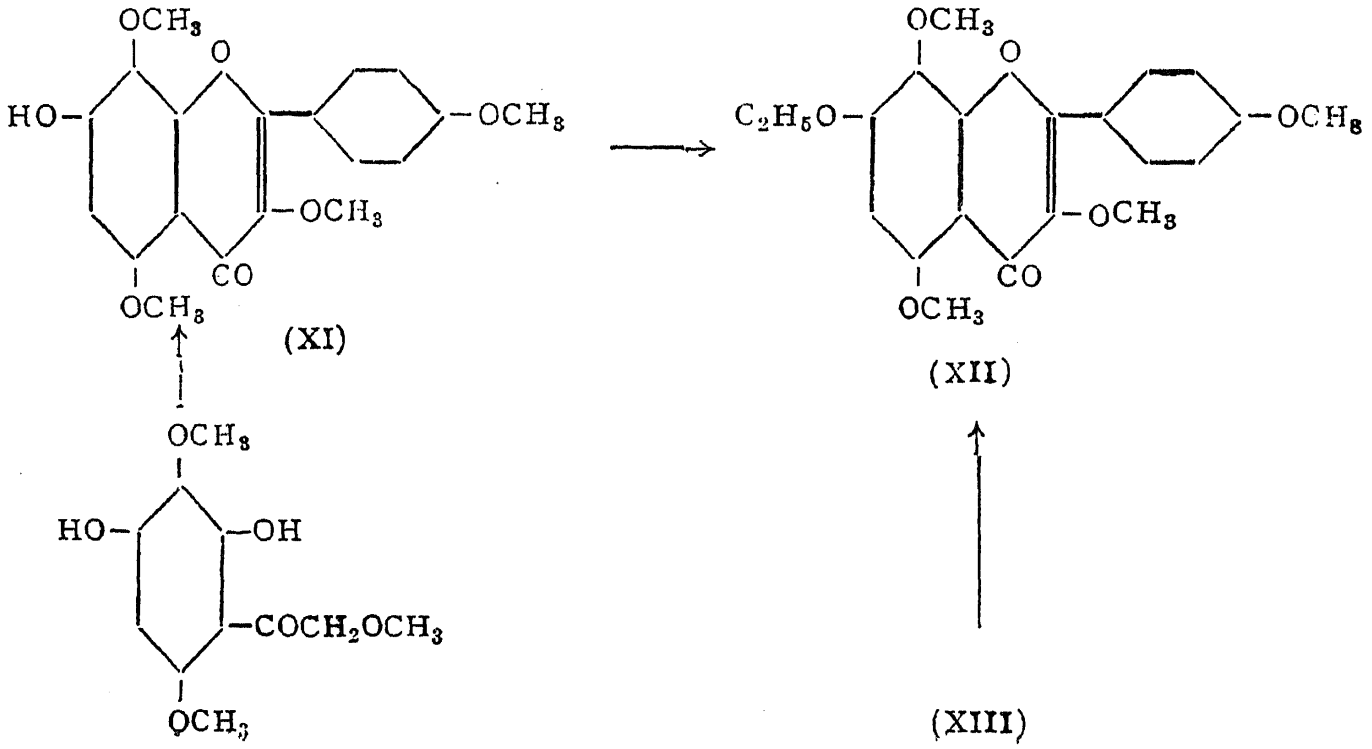
In view of the disagreement mentioned above it was felt necessary to make sure of the constitution of the synthetic trimethyl ether. For this purpose it was ethylated completely and its diethyl-ether obtained. This was found to be identical with 3:8:4′-trimethoxy-5:7-diethoxy flavone synthesised in the following manner. 3:4′-O-dimethyl kaempferol (I) was partially ethylated. Based on analogy with partial methylation of the dimethyl ether[4] in which the 7-position is first affected, the ethyl group is considered to go to this position (VII); the reactions of the compound agree

with this constitution. Subsequent oxidation with persulphate, partial methylation of the quinol (VIII) and final ethylation of (IX) yield the required diethyl-trimethyl herbacetin (X).



Thus it is established that the synthetic trimethyl ether is O-3 : 8 : 4′-trimethyl-herbacetin and that tambulin does not have this constitution.

In order to have an absolutely independent check, the above quinol (VIII) is fully methylated whereby it forms a tetramethyl-mono-ethyl ether which should be 3 : 5 : 8 : 4′-tetramethoxy-7-ethoxy flavone. This is confirmed by comparing it with the ethylation product of 7-hydroxy-3 : 5 : 8 : 4′-tetramethoxy flavone obtained by the method of Goldsworthy and Robinson[6]



as a stage in the earlier synthesis of herbacetin. They are found to be identical.

Experimental

3 : 4′-Dimethoxy-5-hydroxy-7-benzyloxy-flavone (II)

3 : 4′-dimethyl ether of kaempferol (I) (1·0 g.) was dissolved in dry acetone (50 c.c.) and anhydrous potassium carbonate (6·0 g.) and benzyl chloride (0·38 c.c.; 1 mol.) added. The mixture was refluxed for 20 hours, the potassium salts were then filtered off and washed with hot acetone. Acetone was removed by distillation from the filtrate and water added to the residue. A semi-solid separated out. The supernatant water layer was removed by decantation and the substance crystallised from a mixture of alcohol and acetone. The product was obtained as pale yellow small rectangular plates melting at 160–62° (Found: C, 70·9; H, 5·3; $C_{24}H_{20}O_6$ requires C, 71·3; H, 5·0%). It was sparingly soluble in aqueous sodium hydroxide and with alcoholic ferric chloride gave a green colour.

5 : 8-Dihydroxy-3 : 4′-dimethoxy-7-benzyloxy-flavone (III)

The above benzyl ether (II) (1·0 g.) was dissolved in pyridine (20 c.c.) and an aqueous solution of sodium hydroxide (0·5 g. in 20 c.c. of water) added. The mixture was stirred by means of a mechanical stirrer while an aqueous solution of potassium persulphate (1·0 g. in 40 c.c. of water) was added gradually during two hours. The solution was set aside overnight, then rendered just acid to congo red by the addition of hydrochloric acid and the unreacted compound that separated out was filtered off. The filtrate was extracted with ether to remove the last traces of the unreacted compound. To the aqueous layer, sodium sulphite (3·0 g.) and concentrated hydrochloric acid (20 c.c.) were added and the solution was kept at 100° for ½ hour by immersing it in a water-bath. The solid product that separated out was extracted with ether. On removing the ether by distillation a bright yellow semi-solid was left behind. It crystallised from alcohol as bright yellow rectangular plates melting at 204–5° (Found: C, 68·9; H, 5·0; $C_{24}H_{20}O_7$ requires C, 68·6; H, 4·8%). It was soluble in aqueous alkali producing a reddish brown solution and with alcoholic ferric chloride it gave a transient green changing to brown.

5-Hydroxy-7-benzyloxy-3 : 8 : 4′-trimethoxy flavone (IV)

The above 5 : 8-dihydroxy-compound (III) (1·0 g.) was dissolved in dry acetone (25 c.c.) and anhydrous potassium carbonate (5·0 g.) and dimethyl sulphate (0·24 c.c.; 1 mol.) were added. The mixture was refluxed for 6 hours. The potassium salts were filtered off and washed with hot acetone.

The filtrate was concentrated over a water-bath as far as possible and water was added to the residue when a pale yellow solid separated out. It was filtered and crystallised from alcohol, when it was obtained as pale yellow tiny plates melting at 145–47° (Found: C, 68·9; H, 5·0; $C_{25}H_{22}O_7$ requires C, 69·1 and H, 5·1%). It was sparingly soluble in aqueous alkali and with alcoholic ferric chloride gave a green colour.

5: 7-*Dihydroxy*-3: 8: 4′-*trimethoxy-flavone* (*V*)

The above 5-hydroxy-compound (IV) (0·5 g.) was treated with glacial acetic acid (2·0 c.c.) and concentrated hydrochloric acid (4·0 c.c.) and the mixture kept at 60° for one hour. It was then diluted with water and set aside. A pale yellow solid slowly separated out. It was filtered and crystallised from alcohol when it was obtained as straw-yellow rectangular plates and needles melting at 248–50° (Found: C, 62·5; H, 5·1; $C_{18}H_{16}O_7$ requires C, 62·8; H, 4·7%). The mixed melting point with tambuletin was depressed. The substance was soluble in aqueous alkali and with ferric chloride produced an olive-green colour in alcoholic solution.

5: 7-*Diacetoxy*-3: 8: 4′-*trimethoxy-flavone*

The 5: 7-dihydroxy compound (0·1 g.) was treated with acetic anhydride (5. c.c.) and a few drops of pyridine. The mixture was kept gently boiling for two hours and poured into water. After all the acetic anhydride was completely decomposed, the separated solid was filtered. It crystallised from dry ethyl acetate as colourless rectangular rods and needles melting at 178–80° (Found: C, 61·7; H, 4·5; $C_{22}H_{20}O_9$ requires C, 61·7; H, 4·7%).

5: 7-*Diethoxy*-8: 3: 4′-*trimethoxy-flavone* (*VI*)

The above 5: 7-dihydroxy compound (V) (0·4 g.) was dissolved in dry acetone (25 c.c.) and anhydrous potassium carbonate (5·0 g.) and ethyl iodide (0·5 c.c.) were added. The mixture was refluxed for 30 hours. The potassium salts were filtered off and washed with hot acetone. The filtrate was concentrated over a water-bath as far as possible and the residue was treated with water. A colourless solid separated out. It was filtered and crystallised from aqueous alcohol, when it was obtained as clusters of long fine needles melting at 111–13° (Found: C, 66·2; H, 5·9; $C_{22}H_{24}O_7$ requires C, 66·0; H, 6·0%). It was insoluble in alkali and with alcoholic ferric chloride did not give any colour.

5-*Hydroxy*-7-*ethoxy*-3: 4′-*dimethoxy-flavone* (*VII*)

3: 4′-dimethyl-ether of kaempferol (I) (1·0 g.) was dissolved in dry acetone (50 c.c.) and anhydrous potassium carbonate (8·0 g.) and ethyl

iodide (0·27 c.c.; 1 mol.) were added. The mixture was refluxed for 6 hours and the product worked up as in the previous experiment. It crystallised from alcohol as yellow rectangular plates and prisms melting at 127–29° (Found: C, 67·0; H, 5·2; $C_{19}H_{18}O_6$ requires C, 66·7; H, 5·3%). The substance was sparingly soluble in aqueous alkali and with ferric chloride in alcoholic solution it gave a brownish green colour.

5 : 8-*Dihydroxy-7-ethoxy-3 : 4′-dimethoxy-flavone* (*VIII*)

The above compound (VII) (1·6 g.) was dissolved in pyridine (40 c.c.) and sodium hydroxide solution (1·0 g. in 20 c.c. of water) was added. The mixture was stirred while an aqueous solution of potassium persulphate (2·0 g. in 40 c.c. of water) was added gradually during 2 hours. The product was worked up as in similar oxidations already described. It crystallised from alcohol as bright yellow rectangular plates and short needles melting at 168–70° (Found: C, 63·4; H, 5·0; $C_{19}H_{18}O_7$ requires C, 63·7; H, 5·0%). With alcoholic ferric chloride the substance produced a brown colour and in alkali it dissolved giving a reddish brown solution.

5-*Hydroxy-7-ethoxy-3 : 8 : 4′-trimethoxy-flavone* (*IX*)

The 5 : 8-dihydroxy-compound (VIII) (0·5 g.) was dissolved in dry acetone (25 c.c.) and anhydrous potassium carbonate (5·0 g.) and dimethyl sulphate (0·14 c.c.) were added. The mixture was refluxed for 6 hours and worked up as in methylations already described. The product crystallised from alcohol as pale yellow clusters of fine, long needles melting at 172–73° (Found: C, 64·5; H, 5·2; $C_{20}H_{20}O_7$ requires C, 64·5; H, 5·4%). It was sparingly soluble in alkali and with alcoholic ferric chloride, it gave an emerald green colour.

5 : 7-*Diethoxy-3 : 8 : 4′-trimethoxy-flavone* (*X*)

The 5-hydroxy-compound (IX) (0·3 g.) was dissolved in dry acetone (25 c.c.) and anhydrous potassium carbonate (5·0 g.) and ethyl iodide (0·5 c.c.) were added. The mixture was refluxed for 30 hours. The product was crystallised from aqueous alcohol when it was obtained as colourless clusters of long, fine needles melting at 111–13° (Found: C, 66·2; H, 5·9; $C_{22}H_{24}O_7$ requires C, 66·0; H, 6·0%). The substance was insoluble in alkali and with ferric chloride did not give any colour in alcoholic solution. The mixed melting point with compound (VI) was not depressed.

7-*Ethoxy-5 : 8 : 3 : 4′-tetramethoxy-flavone* (*XII*)

(1) The 5 : 8-dihydroxy-3 : 4′-dimethoxy-7-ethoxy flavone (VIII) (0·1 g.) was methylated in dry acetone (25 c.c.) using anhydrous potassium carbonate

(5·0 g.) and dimethyl sulphate (0·3 c.c.). The mixture was refluxed for 30 hours. The colourless product crystallised from alcohol as clusters of short fine needles melting at 160–161°. It did not give any colour with alcoholic ferric chloride and was insoluble in aqueous alkali.

(2) The 7-hydroxy-3 : 5 : 8 : 4′-tetramethoxy-flavone (XI) (0·2 g.) (Goldsworthy and Robinson[6]) was ethylated in dry acetone (25 c.c.) using anhydrous potassium carbonate (5·0 g.) and ethyl iodide (0·3 c.c.). The mixture was refluxed for 30 hours. The product crystallised from alcohol as clusters of short fine needles melting at 160–61° (Found: C, 65·2; H, 5·5; $C_{21}H_{22}O_7$ requires C, 65·3; H, 5·7%). It was insoluble in alkali and did not give any colour with alcoholic ferric chloride. The mixed melting point with the compound prepared in (1) was undepressed.

Summary

According to Bose and Bose[2] tambulin should be 3 : 8 : 4′-trimethyl-ether of herbacetin. A compound of this constitution has now been synthesised from 3 : 4′-dimethyl-ether of kaempferol. Its properties differ markedly from those of tambulin. The constitution of the latter should therefore be considered as still unsettled. The nature of the synthetic substance has been confirmed by preparing its diethyl-ether and proving its identity with 3 : 8 : 4′-trimethyl-5 : 7-diethyl-ether of herbacetin prepared by an independent method.

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