SYNTHETIC EXPERIMENTS IN THE BENZOPYRONE SERIES

Part LIV. Nuclear Methylation of Simple Flavonols

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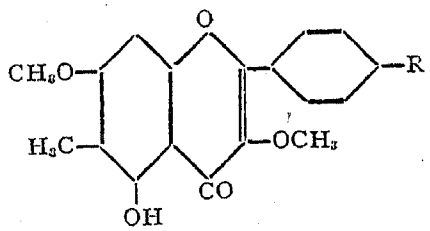
THE nuclear methylation of quercetin has been recently reported.[1] In order to get further information that may lead to a clearer understanding of the reaction, simpler flavonols have now been investigated by the same procedure.

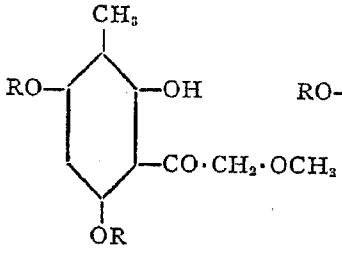
Attempts to effect nuclear methylation of 7-hydroxy-3-methoxy flavone have been unsuccessful. Only O-methylation took place, giving rise to 3 : 7-dimethoxy flavone. When galangin-3-methyl ether was methylated in this way, besides galangin di- and trimethyl ethers, one C-methylated product identical with the synthetic sample of 6-C-methyl-5-hydroxy-3 : 7-dimethoxy flavone (I) was obtained in about 12% yield. Using kaempferol-3 : 4′-dimethyl ether, three products, kaempferol-3 : 7 : 4′-trimethyl ether (m.p., 154–55°), kaempferol tetramethyl ether (m.p., 165–66°) and 6-C-methyl kaempferol-3 : 7 : 4′-trimethyl ether (II, m.p., 182–83°) have been obtained. In another experiment using excess of reagent and heating for a longer period, the trimethyl ethers were not obtained and the product consisted of a mixture of kaempferol tetramethyl ether and 6-C-methyl kaempferol tetramethyl ether (m.p., 163–64°). Methylation with methyl iodide and methanolic potash was also earlier carried out in the case of kaempferol and kaempferide by Ciamician and Silber[2] and by Waljaschko.[3] They obtained three products (m.p., 175–76°, 154–55°, 139–40°) the first two of which would appear to be identical with 6-C-methyl kaempferol-3 : 7 : 4′-trimethyl ether (II) and kaempferol-3 : 7 : 4′-trimethyl ether respectively. A fraction corresponding to the third product (139–40°) can be easily isolated even in our



I, R = H; II, R = OCH_3

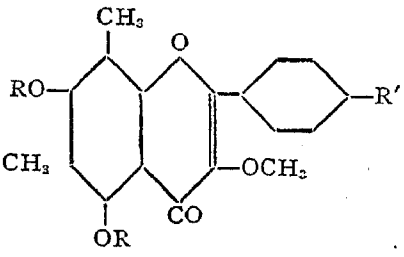
experiment. But it is found to be a mixture consisting of kaempferol tri- and tetramethyl ethers.

The preparation of reference compounds was made just as in the experiments relating to quercetin.[1] Starting with 2-hydroxy-3-methyl-ω:4:6-trimethoxy acetophenone (III), 8-C-methyl derivatives of galangin trimethyl ether (IV) and kaempferol tetramethyl ether (V) were obtained by two methods: (1) the Allan-Robinson condensation using the anhydride and sodium salt of benzoic or anisic acid and (2) the chalkone method using benzaldehyde or anisaldehyde and subsequent dehydrogenation. When C-methyl-ω-methoxy-phloracetophenone[1] (VI) was itself employed for the Allan-Robinson condensation, a mixture was obtained in each case, the 8-C-methyl compounds (VII) and (VIII) being the major products and the 6-C-methyl ones (IX and X) the minor. Demethylation could be conveniently effected using hydriodic acid which did not cause isomerisation under the ordinary conditions employed and the 8-C- and 6-C-methyl galangins and kaempferols obtained.



III, R=CH_3

VI, R=H

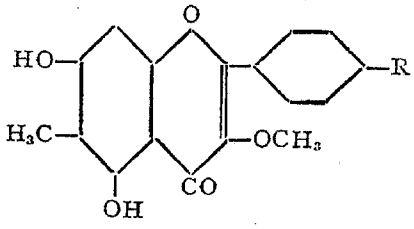


IV, R=CH_3; R′=H

V, R=CH_3; R′=OCH_3

VII, R=R′=H

VIII, R=H; R′=OCH_3



IX, R=H

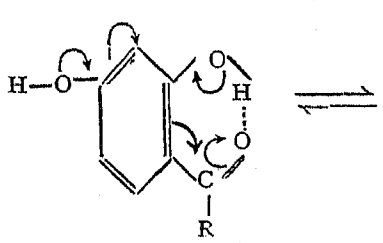
X, R=OCH_3

Recently a detailed study of the nuclear methylation of the following chromone derivatives has been made: chromones,[4,5] flavones,[5,6] flavonols,[7,1] and isoflavones.[8] In all these cases nuclear methylation has been definitely shown to take place in the 6-position. This may appear to be extraordinary because in 7-hydroxy and 5:7-dihydroxy chromone derivatives, the 8-position is the most active in all other reactions. It is therefore obvious that the conditions of nuclear methylation are somewhat unique and are different from other reactions.

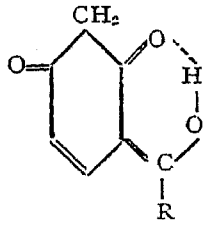
Since 3-methoxy-7-hydroxy flavone does not undergo nuclear methylation, it follows that a single hydroxyl group in the 7-position is not enough for this reaction though it is sufficient for others. The simultaneous presence of two hydroxyl groups in the 5- and 7-positions is found to be essential. This arrangement of functional groups which is the same as

present in resacetophenone seems to provide the minimum requirement of this reaction. This point has now been established by the experiments using *p*-hydroxy acetophenone and isopeonol which like peonol (*cf.*, Crabtree and Robinson[9]) do not undergo nuclear methylation. Another highly significant new observation has been made now in the case of galangin-3-methyl ether. When it is methylated with methyl iodide and methanolic sodium methoxide for a shorter period (3 hr.), 6-C-methyl galangin 3-methyl ether (IX) can be isolated as one of the products. This definitely represents the first stage of the reaction and has not so far been isolated in any other case and it supports the earlier contention of Crabtree and Robinson[9] that C-methylation should precede O-methylation of the *para*-hydroxyl group.

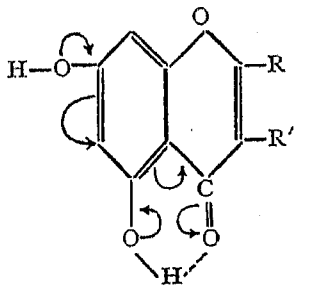
An earlier explanation of nuclear methylation[10] related to resorcinol derivatives and was based on analogy with the C-methylation of acetoacetic ester. The emphasis was then placed on the behaviour of the *p*-hydroxy group undergoing isomeric change to yield a ketonic form and the carbonyl group outside the nucleus was considered to exert its effect through the ring double bonds. The experiments described in this paper emphasise the need for the presence of a free *ortho*-hydroxy group also functioning by virtue of its capacity to develop ketonic properties and this is possible through the medium of hydrogen bond formation as indicated in the formulæ XI to XIV. It follows then that carbonyl compounds of resorcinol and 5:7-dihydroxy flavone derivatives function like diketones and undergo nuclear



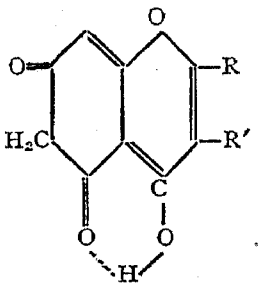
XI



XII



XIII



XIV

methylation. The results obtained in the course of the large volume of experimental work done in the past seems to confirm the idea that the greater the capacity of the molecule to assume the ketonic form, the greater the amount of nuclear methylation. For example, phloroglucinol derivatives undergo nuclear methylation with considerable ease.

EXPERIMENTAL

8-*Methyl-O-trimethyl galangin* (*IV*)

An intimate mixture of 2-hydroxy-3-methyl-ω : 4 : 6-trimethoxy acetophenone (III) (3 g.), benzoic anhydride (18 g.) and sodium benzoate (3·5 g.) was heated at 180–84° for four hours under diminished pressure, refluxed with alcoholic potash (7%, 150 c.c.) for half an hour and alcohol removed under vacuum. The remaining mixture was diluted with water and the solid product filtered and washed with water. It crystallised from dilute alcohol as colourless rectangular rods and prisms melting at 159–60° (Found: C, 69·6; H, 5·1; $C_{19}H_{18}O_5$ requires C, 69·9; H, 5·5%). A sample was also made by the chalkone method adopted by Lindstedt and Misiorny.[11] The two samples were identical and the mixed melting point was undepressed.

8-*C-Methyl galangin*

8-C-Methyl galangin trimethyl ether (1 g.) was refluxed with acetic anhydride (5 c.c.) and hydriodic acid (d., 1.7; 15 c.c.) for two hours and the product was poured into an ice-cold solution of sodium bisulphite and then extracted with ether. The ether solution was in turn extracted with 5% aqueous sodium carbonate and the alkaline solution neutralised. The pale yellow precipitate crystallised from methyl alcohol as yellow needles and rectangular plates melting at 262–63°. Yield, 0·5 g. (Found: C, 67·1; H, 4·1; $C_{16}H_{12}O_5$, requires C, 67·6; H, 4·2%). It yields an yellow solution with alkali and an olive brown colour turning olive green with ferric chloride. The acetate crystallised from alcohol as colourless needles melting at 183–84°.

The substance was boiled with excess of dimethyl sulphate and dry potassium carbonate in acetone medium until it gave negative ferric reaction (60 hr.). The acetone solution was filtered, concentrated and then treated with a little petroleum ether. The solid that separated crystallised from aqueous alcohol as colourless rectangular rods and prisms, melting at 159–60° alone or when mixed with an authentic sample of 8-methyl galangin trimethyl ether (IV).

Allan-Robinson Condensation of C-methyl-ω-methoxy phloracetophenone (VI) with benzoic anhydride and sodium benzoate

A well powdered mixture of the ketone (5 g.), anhydride (30 g.) and sodium salt (6 g.) was heated at 180–84° under reduced pressure and the product hydrolysed with 8% alcoholic potash, diluted with water and then saturated with carbon dioxide. The yellow solid (4·1 g.) thus obtained melted between 204–45°; it was dissolved in the minimum amount of methyl alcohol and the solution allowed to cool at room temperature. The solid that separated out was marked fraction A and that present in solution, fraction B.

Fraction A: 6-*C-Methyl*-3-*O-methyl galangin* (*IX*)

Fraction A was repeatedly crystallised from methyl alcohol; pale yellow needles and prisms, m.p. 273–74°. Yield, 1·0 g. It was acetylated by the acetic anhydride-pyridine method; the acetate crystallised from ethyl acetate-potroleum ether mixture as colourless needles melting at 167–68°. This on deacetylation with alcoholic hydrochloric acid (1 : 1) yielded pure 6-C-methyl-3-O-methyl galangin which crystallised from methyl alcohol as very pale yellow aggregates of tiny needles and prisms melting at 274·75° (Found: C, 68·1; H, 4·7; $C_{17}H_{14}O_5$ requires C, 68·5; H, 4·7%). It gives a green colour with ferric chloride and a bright yellow solution with sulphuric acid or alkali.

6-*C-Methyl galangin trimethyl ether*

The above 3-methyl ether was methylated with excess of dimethyl sulphate using potassium carbonate and acetone. The complete methyl ether crystallised from methyl alcohol as colourless rectangular needles and plates, melting at 160–61° which was depressed to 140° when mixed with the synthetic sample of 8-C-methyl galangin-trimethyl ether. (Found: C, 69·5; H, 5·9%).

6-*C-Methyl*-3 : 7-*O-dimethyl galangin* (*I*)

The 3-methoxy flavone (IX) (0·2 g.) in acetone solution was refluxed with dimethyl sulphate (0·07 c.c., 1 mole) and anhydrous potassium carbonate (0·5 g.) for 12 hours. Acetone was distilled off and water added to dissolve the potassium salts. The insoluble solid was filtered and washed with aqueous sodium carbonate and with water. It crystallised from methyl alcohol as pale yellow elongated rhombohedral prisms, melting at 165–66° (Found: C, 68·8; H, 4·8; $C_{18}H_{16}O_5$ requires C, 69·2; H, 5·1%). It is sparingly soluble in alkali and gives a green colour with alcoholic ferric

chloride. The acetate crystallised from ethyl acetate-petroleum ether mixture as colourless shining aggregates of small prisms melting at 183–84°.

6-C-Methyl galangin

The 3-methyl ether (IX) was demethylated with hydriodic acid in the usual way; the product crystallised from ethyl acetate as yellow rectangular plates melting at 228–30° (Found: C, 68·1; H, 4·1; $C_{16}H_{12}O_5$ requires C, 67·6; H, 4·2%). It dissolves in alkali or concentrated sulphuric acid to an yellow solution and yields an olive green colour with alcoholic ferric chloride. The acetate crystallised from ethyl alcohol as colourless small prisms and prismatic needles, melting at 165–66°.

Fraction B: 8-*C-methyl*-3-*O-methyl galangin* (*VII*)

The solid (fraction B) was dissolved in the minimum amount of methyl alcohol and the solution cooled when a yellow solid (3·0 g.) (m.p., 221–26°) separated out. It was converted into its acetate which crystallised from ethyl acetate-petroleum ether mixture as colourless long prismatic needles, melting at 185–87°. The pure acetate was deacetylated by refluxing it with alcoholic hydrochloric acid (1 : 1); the product crystallised from methyl alcohol as elongated lens-shaped crystals melting at 235–37° (Found: C, 69·0; H, 4·5; $C_{17}H_{14}O_5$ requires C, 68·5; H, 4·7%). It is highly soluble in alcohol, acetone and ethyl acetate and gives a green colour with alcoholic ferric chloride. Complete demethylation with hydriodic acid and methylation in the usual way yielded 8-methyl galangin and its trimethyl ether respectively, agreeing in their behaviour with the samples prepared earlier.

8-*C-Methyl*-3 : 7-*O-dimethyl galangin*

Methylation of 8-C-methyl galangin and 8-C-methyl-3-O-methyl galangin with two moles and one mole of dimethyl sulphate respectively using dry potassium carbonate and acetone gave a solid which when crystallised twice from methyl alcohol melted at 157–58° (Found: C, 69·3; H, 5·0; $C_{18}H_{16}O_5$ requires C, 69·2; H, 5·1%). It imparts a pale green colour to alcoholic ferric chloride and is sparingly soluble in aqueous alkali. The acetate crystallised from ethyl acetate-petroleum ether mixture as colourless rectangular prisms, melting at 195–97°.

Nuclear methylation of galangin-3-methyl ether

(*a*) *Using methanolic sodium methoxide.*—To a cold solution of sodium methoxide (from 7·5 g. of sodium) in absolute methanol (200 c.c.) was added 5:7-dihydroxy flavonol (5 g.) and the resulting deep reddish brown

solution refluxed with methyl iodide (20 c.c.) for 3 hours. Methyl alcohol and methyl iodide were then removed under vacuum and the residue was diluted with water, acidified and extracted with ether containing a little chloroform. The extract was washed with water and evaporated to dryness. The solid left behind was extracted with 5% aqueous sodium carbonate (solid A). The sodium carbonate solution after acidification yielded a pale yellow solid (0·4 g.) which after repeated crystallisations from methyl alcohol formed pale yellow aggregates of tiny needles and melted at 273–74° alone or when mixed with an authentic sample (mentioned earlier) of 3-methoxy-5 : 7-dihydroxy-6-C-methyl flavone (IX); the acetates also agreed.

The solid (A) was extracted with boiling benzene to remove the completely methylated flavone and the remaining sodium salt was acidified when a pale yellow crystalline solid separated out. It was collected and crystallised from a large amount of alcohol. The first crop after further crystallisation from methanol gave a product (100 mg.) identical with 6-C-methyl-3 : 7-O-dimethyl galangin. The alcoholic mother liquor yielded a solid (3·5 g.) which after recrystallisation melted at 142–44° and yielded a deep brown colour with alcoholic ferric chloride. In its properties, it resembles galangin-3 : 7-dimethyl ether. The benzene extract yielded only galangin trimethyl ether (0·2 g.); m.p., 195–96°.

(*b*) *Using methanolic potash.*—Galangin-3-methy ether (5 g.) in methanol (75 c.c.) and methyl iodide (40 c.c.) was boiled with a solution of potassium hydroxide (8 g.) in methyl alcohol (40 c.c.), 2 c.c. added at a time during 2 days. The solvent was distilled off under reduced pressure, the residue was diluted with water and acidified. The solid that separated out was filtered, and boiled with 5% aqueous sodium carbonate (150 c.c.) for 15 minutes. The solution on acidification did not yield any crystallisable material; the undissolved solid (5·4 g.) was extracted in a soxhlet with dry benzene (Benzene solution A). The insoluble portion (1·5 g.) was boiled with dilute acid and the solid collected. Fractional crystallisation from methyl alcohol yielded two products. The sparingly soluble one (0·6 g.) was identical with 6-C-methyl-3 : 7-O-dimethyl galangin (I) (m.p., 165–66°; acetate, m.p. 183–84°) while the more soluble one was galangin dimethyl ether.

The benzene solution (A) was concentrated when an almost colourless solid was obtained. It crystallised from alcohol as colourless needles melting at 193–94° undepressed by an authentic sample of galangin trimethyl ether.

2-Hydroxy-3-methyl-α- : 4 : 6 : 4′*-tetramethyl chalkone*

A mixture of 2-hydroxy-3-methyl-ω : 4 : 6-trimethoxy acetophenone (III) (1·2 g.) and anisaldehyde (0·68 g.) was dissolved in 8% alcoholic potash

(40 c.c.) and the resulting solution was left corked at room temperature for 48 hours. It was diluted with cold water when some turbidity appeared which was removed by extraction with ether. The aqueous solution was acidified and cooled when a bright yellow product separated out. It was filtered, triturated with aqueous sodium bicrabonate and then with water. The chalkone crystallised from methyl alcohol as small yellow prisms melting at 134–35° (Found: C, 66·9; H, 5·9; $C_{20}H_{22}O_6$ requires C, 67·0; H, 6·1%). Yield, 0·8 g. It gives a reddish-brown colour with ferric chloride and an orange-red solution with concentrated sulphuric acid.

8-C-Methyl-kaempferol tetramethyl ether (V)

(i) A mixture of the above chalkone (0·5 g.) and selenium dioxide (0·5 g.) was treated with dry amyl alcohol (5 c.c.) and then refluxed at 140° for 15 hours. After cooling, it was filtered and the selenium residue on the filter paper was washed with boiling rectified spirits. Amyl alcohol was distilled off under vacuum and the last traces removed by steam distillation. The residue was washed with a little petroleum ether and then crystallised from ethyl acetate-petroleum ether mixture. 8-Methyl kaempferol tetramethyl ether separated as colourless needles, m.p. 191–92°. Yield, 0·3 g. (Found: C, 66·8; H, 5·3; $C_{20}H_{20}O_6$ requires C, 67·4; H, 5·6%).

(ii) 2-Hydroxy-3-methyl-ω: 4: 6-trimethoxy acetophenone (III) (2 g.), anisic anhydride (15 g.) and sodium anisate (2.5 g.) were condensed by the Allan-Robinson method; the product (1·5 g.) crystallised from ethyl acetate-petroleum ether mixture as colourless needles, m.p. 191–92° alone or mixed with the above sample.

8-C-Methyl kaempferol

The above tetramethyl ether (0·5 g.) was refluxed with hydriodic acid (d., 1·7; 8 c.c.) and acetic anhydride (5 c.c.) for 3 hours; the product crystallised from methyl alcohol as pale yellow aggregates of small needles melting at 284–86° (Found in the sample dried at 110° *in vacuo*: C, 63·9; H, 4·2; $C_{16}H_{12}O_6$ requires C, 64·0; H, 4·0%). It gives an olive brown colour with ferric chloride. The acetate crystallised from ethyl acetate-petroleum ether mixture as colourless long needles and rectangular prisms melting at 216–17°. When the tetrahydroxy flavone was re-methylated by the potassium carbonate-acetone method, the product was found to be identical with 8-C-methyl kaempferol tetramethyl ether.

Allan-Robinson Condensation of C-methyl-ω-methoxy phloracetophenone (VI) with anisic anhydride and sodium anisate

The ketone (6 g.), anhydride (36 g.) and sodium salt (6 g.) were condensed by the Allan-Robinson method and the product was fractionally crystallised

from methyl alcohol. The sparingly soluble solid melting at 268–73° was marked fraction A and the more soluble one (m.p., 208–20°) fraction B.

Fraction A: *6-C-methyl-3 : 4'-O-dimethyl kaempferol* (*X*)

It was converted into its acetate which formed colourless needles and rectangular rods (m.p., 191–92°) when crystallised from ethyl acetate-petroleum ether mixutre. The acetate was hydrolysed with alcoholic hydrochloric acid (1 : 1) and the product crystallised from methyl alcohol; pale yellow needles, m.p. 276–77°. Yield, 0·85 g. (Found: C, 65·5; H, 5·1; $C_{18}H_{16}O_6$ requires C, 65·9; H, 4·9%).

6-C-Methyl-O-tetramethyl kaempferol

Compound (X) (0·1 g.) was refluxed with dimethyl sulphate (excess, 0·8 c.c.) and potassium carbonate (5 g.) until it gave negative ferric reaction (80 hours); the product crystallised from ethyl acetate-petroleum ether mixture as colourless rectangular plates melting at 163–64°. This m.p. was considerably depressed when mixed with synthetic 8-C-methyl-O-tetramethyl kaempferol (Found: C, 66·9; H, 5·4; $C_{20}H_{20}O_6$ requires C, 67·4; H, 5·6%).

6-C-Methyl-3 : 7 : 4'-O-trimethyl kaempferol (*II*)

6-C-Methyl-kaempferol dimethyl ether (X) (0·24 g.) in acetone solution (100 c.c.) was refluxed with dimethyl sulphate (0·08 c.c.) and potassium carbonate (0·5 g.) for 10 hours and the product was crystallised from ethyl acetate-petroleum ether mixture; yellow rectangular tablets melting at 182–83° (Found: C, 66·5; H, 5·0; $C_{19}H_{18}O_6$ requires C, 66·7; H, 5·3%). The acetate crystallised from alcohol as colourless rectangular rods, m.p. 199–200°.

6-C-Methyl kaempferol

The dimethyl ether (X) (0·25 g.) was refluxed with hydriodic acid (10 c.c.) and acetic anhydride (5 c.c.) for 2 hours. The 6-C-methyl kaempferol crystallised from ether-petroleum ether mixture as small yellow prisms melting at 290–91° (Found: C, 63·8; H, 4·1; $C_{16}H_{12}O_6$ requires C, 64·0; H, 4·0%). It gives a green colour with alcoholic ferric chloride and the acetate crystallised from alcohol as colourless tiny prisms, m.p. 179–80°.

Fraction B: *8-C-methyl-3 : 4'-O-dimethyl kaempferol* (*VIII*)

The solid was acetylated and the product was repeatedly crystallised from alcohol when it was obtained as colourless prismatic needles and rectangular rods melting at 174–75°. It was deacetylated with alcoholic hydrochloric acid (1 : 1) and then crystallised twice from methyl alcohol;

yellow long prismatic needles, m.p. 228–29°. Yield, 2·5 g. (Found: C, 65·3; H, 4·9; $C_{18}H_{16}O_6$ requires C, 65·9; H, 4·9%). Complete demethylation and methylation in the usual way gave 8-C-methyl kaempferol and its tetramethyl ether respectively.

8-C-Methyl-O-3 : 7 : 4′-trimethyl kaempferol

The above flavone (VIII) was methylated with one mole of dimethyl sulphate as described earlier and the product was crystallised from methyl alcohol; pale yellow needles, m.p. 165–66° (Found: C, 67·0; H, 4·3). The acetate crystallised from ethyl acetate-petroleum ether mixture as colourless small prisms melting at 153–54°.

Nuclear methylation of kaempferol-3 : 4′-dimethyl ether

Methyl alcoholic solution of potassium hydroxide (18 g. in 70 c.c.) was added in lots of 2 c.c. during 12 hours to a refluxing methanolic solution of kaempferol-3 : 4′-dimethyl ether (10 g.) and methyl iodide (55 c.c.). Refluxing was continued for 12 hours more and the solvent removed under reduced pressure. The residue was treated with water and the pale yellow crystalline solid (9·2 g.) was collected. The filtrate did not yield anything on acidification. The solid was refluxed with 5% aqueous sodium carbonate (250 c.c.) for 15 minutes and the undissolved solid was filtered. The filtrate did not yield anything after acidification. The dried residue was dissolved in the minimum amount of absolute alcohol and treated with alcoholic potash (1·1 g.) when an orange potassium salt began to separate. Alcohol was removed under vacuum and the residue extracted with dry benzene (Benzene solution B). The insoluble residue (6·5 g.) was treated with hot dilute hydrochloric acid and the product was fractionally crystallised from methyl alcohol. The first crop melted at 171–76° which on twice crystallisation from ethyl acetate melted at 182–83° alone or when mixed with the synthetic sample of 6-C-methyl-3 : 7 : 4′-O-trimethyl kaempferol (II); yield 1 g. The methyl alcoholic mother liquor yielded 3 : 7 : 4′-O-trimethyl kaempferol melting at 154–55°; yield, 4·2 g.

The benzene solution (B) was concentrated and a little petroleum ether added to remove the impurities. The clear solution gave a product which melted at 162–64°. After a few crystallisations from ethyl acetate, it melted at 165–66° alone or when mixed with kaempferol tetramethyl ether; yield, 3·0 g.

Isopeonol (resacetophenone-2-methyl ether)

It was earlier obtained in a poor yield along with peonol by the Hoesch condensation of resorcinol monomethyl ether and acetonitrile[12] or by Fries migration of O-monomethyl resorcinol acetate.[13] Now it has been

prepared by partial benzoylation of the 4-hydroxy group, methylation and subsequent debenzoylation as follows: 4-O-Benzoyl resacetophenone (m.p., 107–08°) (10 g.) was refluxed in dry acetone solution with methyl iodide (30 c.c.) and anhydrous potassium carbonate (50 g.) during 30 hours on a water-bath. After removal of solvents, water was added to the residue and the resulting mixture was extracted with ether. The ether residue was kept in 8% methyl alcoholic potash (250 c.c.) at room temperature for 3 hours, refluxed for half an hour, neutralised and methyl alcohol was evaporated in vacuum. The residue was extracted with ether and the ether solution was washed with sodium bicarbonate solution and extracted with aqueous sodium hydroxide. The alkaline solution was acidified and the resulting solid crystallised from aqueous alcohol when colourless needles melting at 139–40° separated. Yield, 5·5 g. (Found: C, 64·9; H, 6·2; $C_8H_{16}O_3$ requires C, 65·1; H, 6·0%). Hoesch reported its m.p. as 137°.

Summary

3-Methoxy-7-hydroxy flavone does not undergo nuclear methylation. Nuclear methylation of (1) 3-O-methyl galangin and (2) 3:4′-O-dimethyl kaempferol has been shown to take place in the 6-position. As an intermediate in the case of (1) 3-O-methyl-6-C-methyl galangin has been isolated. The minimum structural requirements of this reaction and its mechanism are discussed.

References

1. Jain and Seshadri .. *J.S.I.R.*, 1951, **13B**, 539.
2. Ciamician and Silber .. *Ber.*, 1899, **32**, 863.
3. Waljaschko .. *Archiv. Pharm.*, 1909, **247**, 453.
4. Whalley .. *J.A.C.S.*, 1952, **74**, 5795.
5. Mukerjee and Seshadri .. *Proc. Ind. Acad. Sci.*, 1953, **38A**, 208.
6. Bannerjee and Seshadri .. *J.S.I.R.*, 1954, **13B**, 598.
7. Jain and Seshadri .. *Ibid.*, 1953, **12B**, 564.
8. Mehta, Seshadri and Varadarajan .. *Proc. Ind. Acad. Sci.*, 1953, **38A**, 381.
   Iengar, Mehta, Seshadri and Varadarajan *J.S.I.R.*, 1954, **13B**, 166.
   Mehta and Seshadri *J.C.S.*, 1954, under publication.
9. Crabtree and Robinson .. *Ibid.*, 1918, **113**, 868.
10. Seshadri and Venkateswarlu .. *Proc. Ind. Acad. Sci.*, 1941, **14A**, 297.
11. Lindstedt and Misiorny .. *Acta. Chem. Scand.*, 1951, **5**, 1213.
12. Hoesch .. *Ber.*, 1915, **48**, 1126.
13. Baker .. *J.C.S.*, 1934, 1691.