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# METHYLENATION STUDIES OF HYDROXYFLAVONOIDS AND DERIVATIVES OF RESORCINOL

## SYNTHESES OF BIFLAVONYLS OF NOVEL TYPES

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**Abstract**—Methylenation of 7-hydroxyflavonoids and carbonyl derivatives of resorcinol in the presence of potassium carbonate and acetone yields bimolecular compounds (II, IV, VI and VIII) linked by a methylenedioxy group in the reactive 7 and 4 positions respectively. Chelated hydroxyls do not enter into this reaction. Methylenation of resacetophenone and 2,4-dihydroxyphenyl benzyl ketone in the presence of ethanolic ethoxide yields nuclear methylenated products having biphenylmethane structures (XII and XIV); coupling occurs in the 3-position of the ketones. The structure of these bis compounds is discussed in relation to the other known types.

METHYLENATION may be regarded as a common natural process. In the group of plant phenolics, methylenation of a catechol unit is often encountered particularly in lignans, alkaloids and some flavonoids.[1-9] In the laboratory, methylenation appears simple when there are only two hydroxyl groups *ortho* to each other in a molecule, but when other hydroxyl groups are present, there is a possibilty of competing reactions. Preferential methylenation of a catechol unit in 6,7 positions was successful in 5,6,7,4′-tetrahydroxy-isoflavone[10] and vogoletin.[11] Generally in flavones and isoflavones, the resistant 5-hydroxyl group does not interfere. 7-Hydroxy compounds when heated with methylene iodide in the presence of potassium carbonate and acetone readily form bimolecular products linked by a methylenedioxy group. The results of this investigation are the following:

### *Inter-O-methylenation*

(i) *Flavanones.* Methylenation of 5,7-dihydroxyflavanone (Ia) and naringenin (Ib) with one mole of methylene iodide in the presence of potassium carbonate and acetone yields products which have been assigned structures IIa and IIb respectively. The presence of a methylenedioxy group in these compounds is indicated by the

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[1] K. W. Gopinath, A. R. Kidwai and L. Prakash, *Tetrahedron* **16**, 201 (1961).

[2] L. Crombie and D. A. Whiting, [a]*Tetrahedron Letters* No. 18, 801 (1962); [b]*J. Chem. Soc.* 1569 (1963).

[3] W. Cocker, T. Dahl, C. Dempsey and T. B. H. McMurry, *Chem. & Ind.* 216 (1962).

[4] H. Suginome, *Experientia* **15**, 161 (1962).

[5] J. B. von Bradenberg and P. K. Hietala, *Acta Chem. Scand.* **15**, 696, 936 (1961).

[6] B. L. van Duuren, *J. Org. Chem.* **26**, 5013 (1961).

[7] I. A. M. Cruickshank and D. R. Perrin, *Nature, Lond.* **187**, 799 (1960); *J. Amer. Chem. Soc.* **84**, 1922 (1962).

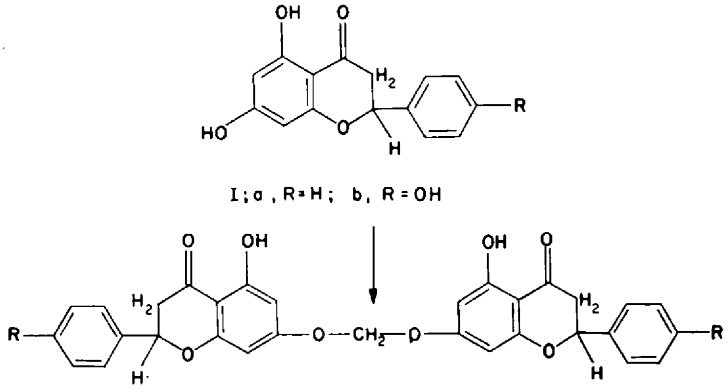
[8] A. J. Birch, B. Moore, S. K. Mukerjee and C. W. L. Bevan, *Tetrahedron Letters* No. 15, 673 (1962).

[9] R. N. Khanna and T. R. Seshadri, *Tetrahedron* **19**, 219 (1963).

[10] S. K. Arora, A. C. Jain and T. R. Seshadri, *Tetrahedron*, **18**, 559 (1962).

[11] S. Rangaswami and H. Rao, *Proc. Indian Acad. Sci.* **A49**, 241 (1959).

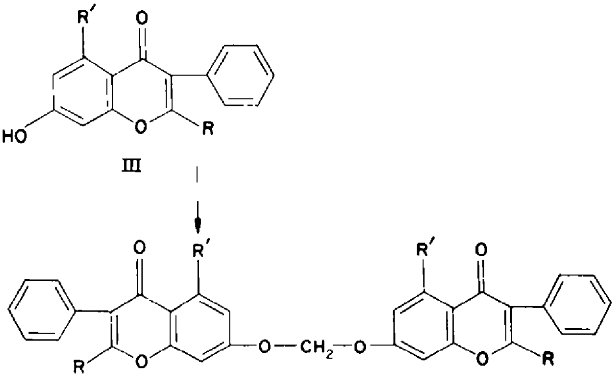
positive gallic acid–sulphuric acid test as well as by a characteristic band at about 1060 cm$^{-1}$ in the IR spectrum.[12] In view of the predominant reactivity of the 7-hydroxyl group as compared with others present in flavanones,[13] it is considered that this group alone takes part in the methylenation. This is confirmed by the insolubility of the product in aqueous sodium carbonate.



I; a, R=H; b, R=OH

II; a, R=H; b, R=OH

(ii) *Isoflavones.* The 7-hydroxyisoflavones (IIIa, b and c) when subjected to methylenation using the potassium carbonate-acetone method readily yield the corresponding bi(7-isoflavonyloxy) methanes (IVa, IVb and IVc) respectively. The bis character of the products was confirmed by the molecular weight determination of IVb by the cryoscopic method. Here also the resistant 5-hydroxyl group does not enter into the reaction.



III

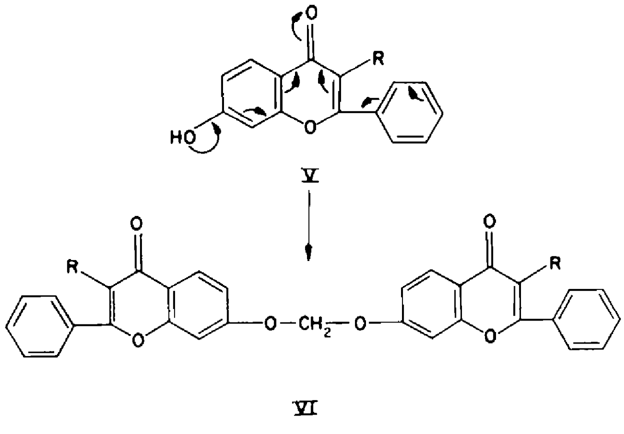
IV

(a) R = R′ = H; (b) R = Me, R′ = H; (c) R = Me, R′ = OH

(iii) *Flavones.* In these compounds the reactivity of the 7-hydroxyl group is reduced, no doubt due to the side phenyl which is also conjugated with the carbonyl group (V). Methylenation required a longer period (ca. 60 hr) in order to convert Va as well as Vb into VIa and VIb respectively.

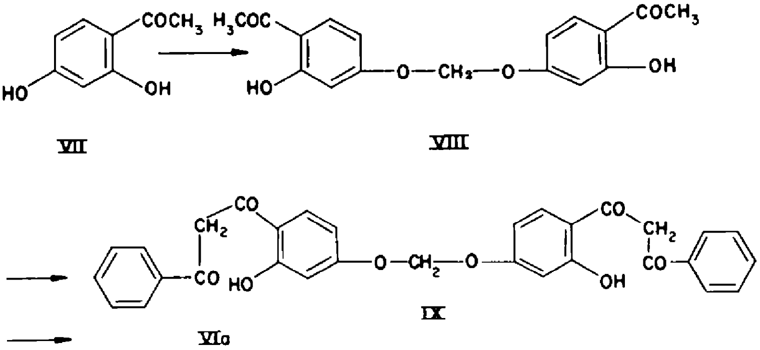
[12] H. Suginome, *Tetrahedron Letters* No. 19, 16 (1960).

[13] N. Narasimhachari and T. R. Seshadri, *Proc. Indian Acad. Sci.* **A32**, 256 (1950).

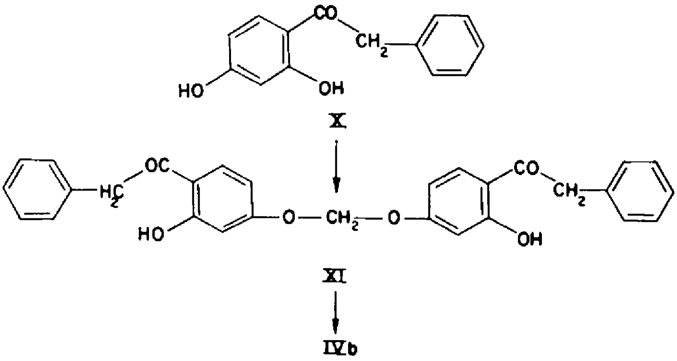


(a) R = H; (b) R = $OCH_3$

(iv) *Carbonyl derivatives of resorcinol.* The product from resacetophenone (VII) proved to be bi(2-hydroxy-acetophenonyl-4-oxy)methane (VIII) by conversion into bi(7-flavonyloxy)methane (VIa) through the bis-diketone (IX) as follows:



Similarly 2,4-dihydroxyphenyl benzyl ketone (X) yielded bi(2-hydroxy-4-deoxybenzoinyl-4-oxy)methane (XI). In conformity with this structure it gives positive ferric chloride and methylenedioxy tests and undergoes the following changes. (i) On heating with aluminium chloride and benzene, X is regenerated; and (ii) When heated with sodium acetate and acetic anhydride, IVb is produced.



### *Occurrence of bimolecular compounds in Nature*

(i) *Carbon-carbon coupling.* In Nature, direct carbon-carbon coupling of two units is fairly common in a variety of compounds.[14–16] In the flavonoids as many as seven biflavonyls are known to occur.[17–19] They contain two flavone units linked in the 3′ and 8″ positions and have been isolated mostly from the leaves of *Gymnosperms* being biapigeninyl derivatives differing only in the position of methoxyl groups. The recent synthesis of ginkgetin confirms the biflavonyl structure.[20]

(ii) *Carbon-oxygen coupling* has been discussed by Erdtman *et al.*[15] One case recently discovered in flavones is hinokiflavone (4′,8″-biapigeninyl ether).[21] Of the three naturally occurring dimeric proanthocyanidins with this type of coupling,[22] one was isolated by Forsyth and Roberts and two similar dimeric compounds by Freudenberg and Weinges. In the coumarins, daphnoretin is an example of C—O—C coupling in a natural compound.[23]

(iii) *Other possible couplings.* Other modes of linking as in biflavonyloxymethanes are capable of easy formation. The biflavonyl methanes in which two flavonoid units are linked by a methylene group, are found in the structures of rottlerin[24] dicoumarol and vilangin.[25] A number of polyhydroxy-biphenylmethane derivatives occurring in ferns[26,27] and in the anthelmintic drug Kousso[28] have similar features.

### *Inter-C-methylenation*

The formation of biflavonyloxymethanes using methylene iodide corresponds to O-methylation and that of biflavonyl methanes to C-methylation. Much of the earlier work on nuclear methylation was carried out on carbonyl derivatives of resorcinol using methyl iodide in the presence of methanolic potash.[29] Hence these compounds have been selected for the study of nuclear methylenation under similar conditions.

(i) *Resacetophenone.* Resacetophenone was methylenated with methylene iodide in the presence of ethanolic sodium ethoxide; ethanol was used instead of methanol generally used for C-methylation because of the poor miscibility of methylene iodide

[14] D. H. R. Barton and T. Cohen, *Festschrift Prof. A. Stoll,* Birkhauser, Basel, 117 (1957).

[15] H. Erdtman and C. Wachtmeister, *Festschrift Prof. A. Stoll,* Birkhauser, Basel, 144 (1957).

[16] C. H. Hassal and A. I. Scott, *Recent Developments in the Chemistry of Natural Phenolic Compounds* (Edited by W. D. Ollis) pp. 119–133. Pergamon Press, London (1961).

[17] W. Baker and W. D. Ollis, *Recent Developments in the Chemistry of Natural Phenolic Compounds.* (Edited by W. D. Ollis) p. 152. Pergamon Press, London (1961).

[18] W. Baker, A. C. M. Finch, W. D. Ollis and K. W. Robinson, *J. Chem. Soc.* 1477 (1963).

[19] G. D. Modica, P. F. Rossi and A. M. River, *Atti accad. nazl. Lincai. Rend. Class sci. Fis. mat, nat.* **27,** 127 (1959); *Chem. Abstr.* **54,** 14235 (1960).

[20] K. Nakazawa and M. Ito, *Tetrahedron Letters* No. 8, 317 (1962); *Chem. and Pharm. Bull.* **10,** 1032 (1962).

[21] T. Sawada, *J. Pharm. Soc. Japan* **78,** 1023 (1958).

[22] K. Freudenberg, *Recent Progress in the Chemistry of Natural and Synthetic Pigments* (Edited by T. S. Gore, B. D. Joshi *et al.*) p. 225. Academic Press, New York (1962).

[23] R. Tschesche, Schacht and G. Legler, *Liebig's Ann.* **662,** 113 (1963).

[24] A. McGookin and A. Robertson, *J. Chem. Soc.* 113 (1948).

[25] C. B. Rao and V. Venkateswarlu, *J. Org. Chem.* **26,** 4529 (1961).

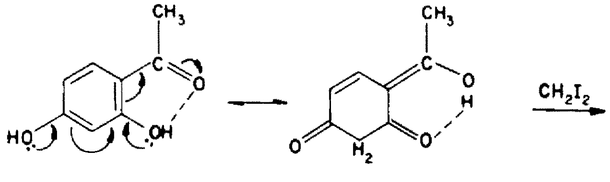
[26] A. Pentilla and J. Sundman, *Acta Chem. Scand.* **15,** 777, 839 (1961).

[27] A. Pentilla and J. Sundman, *Acta Chem. Scand.* **16,** 1251 (1962).

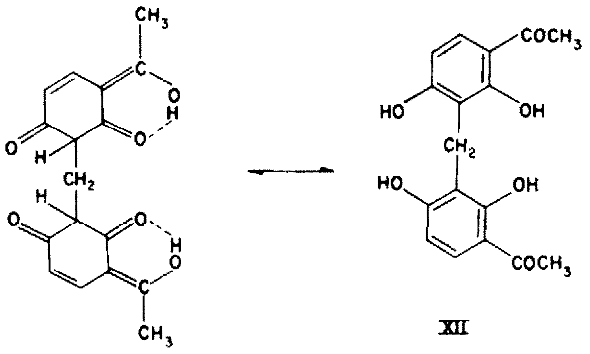
[28] A. J. Birch and A. R. Todd, *J. Chem. Soc.* 3102 (1952).

[29] A. C. Jain and T. R. Seshadri, *J. Sci. Industr. Res., India* **14A,** 227 (1955).

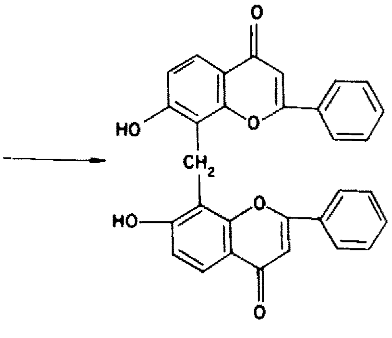
with methanol. The product formed differs from the one obtained by methylenation in the presence of potassium carbonate and acetone, although its composition $C_{17}H_{16}O_6$ is the same as indicated not only by elemental analysis but also by its molecular weight and the molecular weight of the complete methyl ether. The difference is, however, indicated by the formation of a tetramethyl ether and a tetra-acetate showing the presence of four hydroxyl groups. Hence only nuclear methylenation has taken place, the compound having structure XII.



VII

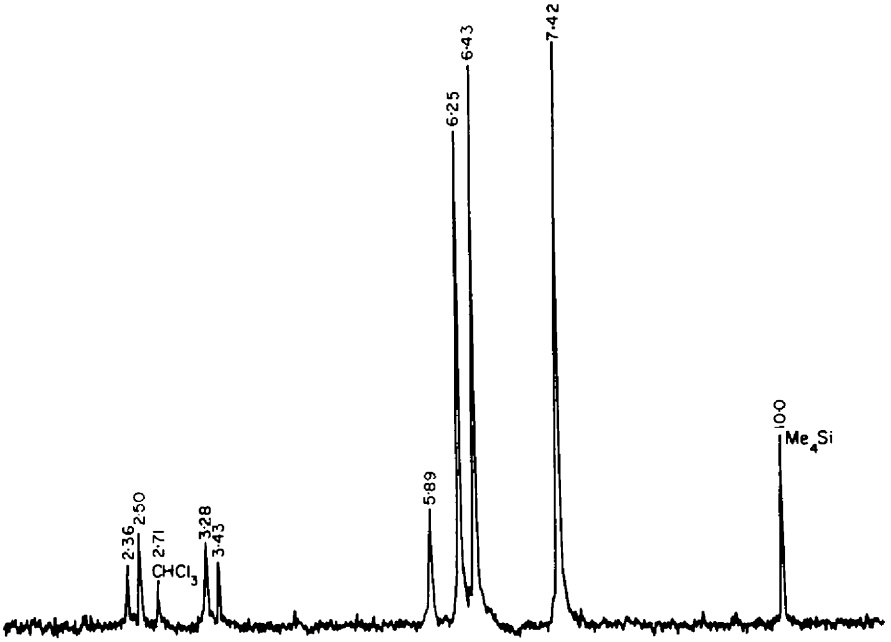


XII



XIII

This formulation is supported by the NMR spectrum of the methyl ether (Diagram I). Thus only four peaks of aromatic protons are shown at τ 2·36, 2·50 and τ 3·28 and 3·43 (the peaks have been marked with reference to tetramethylsilane). A peak at τ 5·89 is equivalent to two protons for the two bridge hydrogen atoms of the diphenylmethane structure. The peaks at τ 6·25 and 6·43 are due to protons of methoxyl groups; this splitting being due to the presence of methoxyl groups adjacent to acetyl groups. The intergration of these peaks shows twelve protons which is consistent with the presence of four methoxyl groups in the methyl ether. The six acetyl protons are shown by a peak at τ 7·42.



NMR spectrum of bi-(2,4-dimethoxy-3-acetophenonyl) methane at 60 Mc in CDCl$_3$ with chemical shifts in τ values.

Diagram 1.

The IR spectrum of the complete methyl ether also supports the structure (XII). The possibilty of O-methylenation taking place was eliminated by the facts that the methylenation product is soluble in aqueous sodium carbonate and does not undergo any change when heated with anhydrous aluminium chloride in benzene even for a long period and it gives a diacetate under mild conditions and a tetra-acetate under more drastic conditions. Further the presence of the acetyl groups was shown by the positive iodoform reaction.

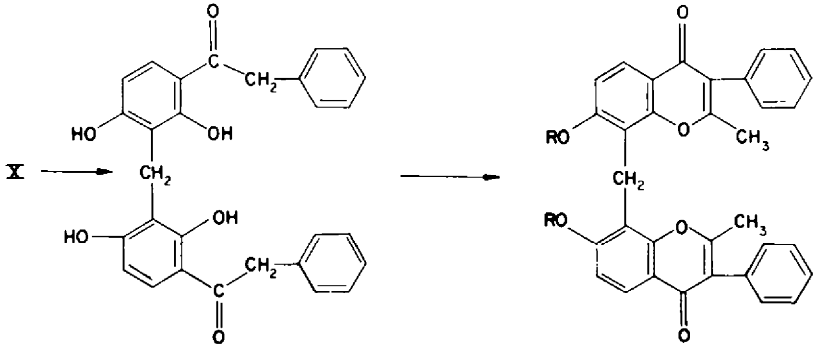
There is, therefore, a marked difference between nuclear methylation and methylenation of resacetophenone. The former results not only in C-methylation but is followed by O-methylation of the reactive phenolic hydroxyl group *para* to carbonyl.[29] This is supported by the isolation of the first stage C-methylated product in the case of 3-O-methylgalangin.[30] In the reaction with methylene iodide, the lack of O-methylenation is probably due to the steric disposition of the hydroxyl groups preventing both intra- and inter-O-methylenation. Construction of models supports this idea.

The C-methylenation product (XII) was converted into bi(7-hydroxy-8-flavonyl) methane (XIII) by heating it with benzoyl chloride, potassium carbonate and acetone and subsequently hydrolysing and cyclizing the diketonyl methane in the presence of alkali. This is the first synthesis of a biflavonyl methane.

(ii) *2,4-Dihydroxyphenylbenzyl ketone* (X). The product of methylenation with

[30] A. C. Jain and T. R. Seshadri, *Proc. Ind. Acad. Sci.* **40A**, 249 (1954).

methylene iodide and ethanolic sodium ethoxide is different from the compound (XI) obtained by methylenation by the potassium carbonate–acetone method. It does not undergo any change when heated with aluminium chloride in benzene medium. Further the elemental analyses of the product and its acetate and methyl ether, the molecular weight of the product and the methoxyl values of the complete methyl ether are consistent with the bis formulation as shown in structure XIV. Finally the methylenated compound yielded bi(2-methyl-7-acetoxy-8-isoflavonyl) methane (XVa) when heated with acetic anhydride and sodium acetate at 170° and this was deacetylated to give bi(2-methyl-7-hydroxy-8-isoflavonyl)methane (XVb).



XIV

XV

(a) R = $COCH_3$
(b) R = H

Chakravarti *et al.*[31] have recently carried out the methylenation of 2,4-dihydroxyphenylbenzyl ketone (X) by the sodium ethoxide method. The product obtained has similar characteristics but they consider that it is 7-hydroxyisoflavanone and claim that this reaction provides a novel method of isoflavone synthesis. This seems to be unlikely in the light of our results. The following properties of the compound further rule out the possibility of its being 7-hydroxyisoflavanone. It gives a positive ferric reaction. It has a low carbonyl frequency (1625 $cm^{-1}$) in the IR spectrum; usually C=O frequency in 5-hydroxyisoflavanones is 1665 $cm^{-1}$.[12] The properties of the compound and its derivatives do not agree with those described for 7-hydroxyisoflavanone and its derivatives by Inoue[32] who prepared them by the catalytic reduction of the corresponding isoflavones.

| | Methylenation product (XIV) | 7-Hydroxyisoflavanone[32] |
|---|---|---|
| m.p. | 191–192° | 175° |
| $\lambda_{max}$ (ethanol) | 260, 326 (inflex. at 295 mμ) | 275, 310 mμ |
| $\nu_{C=O}$ (KBr) | 1625 $cm^{-1}$ | 1665 $cm^{-1}$ |
| Acetate, m.p. | 110–111° | 108·5° |
| D.N.P. derivative, m.p. | 264–265° | 245° |
| Methyl ether, m.p. | 114–115° | 92° |

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[31] D. Chakravarti, S. Chakraborty, N. Chakravarti and N. Roy, *Sci. and Cult.* **27**, 407 (1961).
[32] N. Inoue, *J. Chem. Soc. Japan* **79**, 112 (1958).

Finally the possibility of isoflavanone ring formation as visualized by Chakravarti *et al.* is eliminated by our observation that 2-hydroxy-4-methoxphenyl benzyl ketone does not react with methylene iodide under similar conditions.

In analogy with the experiments on carbonyl derivatives of resorcinol, the 5,7-dihydroxyflavonoids are also expected to yield C-methylenated *bis* compounds; these would be linked in the 6-position. A study of such systems is in progress.

## EXPERIMENTAL

The methylenedioxy test was performed by heating the compound with gallic acid and conc $H_2SO_4$ on a boiling water bath; emerald green colour was taken as a positive reaction. Light petroleum used in all cases had the boiling range 40–60°.

### *Inter-O-methylenation experiments*

*Bi(5-hydroxy-7-flavanonyloxy)methane* (IIa). 5,7-Dihydroxyflavanone[33] (1 g) was refluxed with acetone (50 ml), methylene iodide (0·25 ml, 0·7 mole equiv.) and $K_2CO_3$ (5 g) for 6 hr. Acetone was distilled off and water (100 ml) added to the residue. The solid (0·2 g) after filtration and drying crystallized from ethyl acetate as colourless micro prisms, m.p. 212–213°; it gave a positive methylenedioxy test and a red colour with ethanolic ferric chloride (Found: C, 70·6; H, 4·7; $C_{31}H_{24}O_8$ requires: C, 71·0; H, 4·6%).

*Bi(5,4′-dihydroxy-7-flavanonyloxy)methane* (IIb). Naringenin (0·4 g) on treatment as in the preceding case gave a product (0·1 g) which crystallized from ethanol as colourless small prisms, m.p. 256–257°; it gave a reddish brown colour with ethanolic ferric chloride and a positive methylenedioxy test (Found: C, 65·7; H, 4·5; $C_{31}H_{24}O_{10}$ requires: C, 65·6; H, 4·5%).

*Bi(7-isoflavonyloxy)methane* (IVa). 7-Hydroxyisoflavone[34] (0·2 g) yielded a product (50 mg) which crystallized from acetic acid as colourless plates, m.p. 246–247°; it gave a positive methylenedioxy test. (Found: C, 75·6; H, 4·2; $C_{31}H_{20}O_6$ requires: C, 76·2; H, 4·1%).

*Bi(2-methyl-7-isoflavonyloxy)methane* (IVb). 2-Methyl-7-hydroxyisoflavone[35] (0·6 g), gave a product (0·2 g) which crystallized from benzene as colourless silky needles, m.p. 191–192°; it gave a positive methylenedioxy test (Found: C, 76·5; H, 5·2; mol. wt. 509 (cryoscopic method using benzene). $C_{33}H_{24}O_6$ requires: C, 76·7; H, 4·7%, mol. wt. 516).

*Bi(2-methyl-5-hydroxy-7-isoflavonyloxy)methane* (IVc). 2-Methyl-5,7-dihydroxyisoflavone[35] (0·5 g) yielded a product (0·1 g) which crystallized from ethyl acetate–ethanol as colourless needles, m.p. 169–170°; it gave a brown-red ferric reaction and a positive methylenedioxy test (Found: C, 71·8; H, 4·0; $C_{33}H_{24}O_8$ requires: C, 72·3; H, 4·4%).

*Bi(7-flavonyloxy)methane* (VIa). 7-Hydroxyflavone[36] (0·2 g), acteone (125 ml), methylene iodide (0·1 ml) and $K_2CO_3$ (4 g) were refluxed together for 60 hr. The product (50 mg) crystallized from ethyl acetate as small needles, m.p. 246–247°; it gave a positive methylenedioxy test (Found: C, 75·8; H, 4·3; $C_{31}H_{20}O_6$ requires: C, 76·2; H, 4·1%).

*Bi(3-methoxy-7-flavonyloxy)methane* (VIb). 3-Methoxy-7-hydroxyflavone[37] (0·7 g) was refluxed in dioxane–acetone (50:25 ml) with methylene iodide (0·2 ml) and $K_2CO_3$ (5 g) for 60 hr. The product (0·3 g) crystallized from ethyl acetate as colourless prisms, m.p. 204–205°; it gave a positive methylenedioxy test. (Found: 72·1; H, 4·8; $C_{33}H_{24}O_8$ requires: 72·3; H, 4·4%).

*Bi(2-hydroxy-1-acetophenonyl-4-oxy)methane* (VIII). Resacetophenone (2 g) was refluxed in acetone solution (35 ml) with methylene iodide (1 ml) and $K_2CO_3$ (10 g) for 4 hr. The product (0·5 g) crystallized from ethanol as colourless clusters of needles, m.p. 145–146° with a previous shrinking at 136°; it gave a red colour with ethanolic ferric chloride and a positive methylenedioxy test (Found: C, 65·0; H, 5·0; $C_{17}H_{16}O_6$ requires: C, 64·6; H, 5·1%).

*Bi(7-flavonyloxy)methane* (VIa). The above product (0·55 g) in acetone solution (150 ml) was refluxed with benzoyl chloride (0·5 ml) and $K_2CO_3$ (4 g) for 28 hr. Acetone was distilled off and

[33] J. Shinoda and S. Sato, *J. Pharm. Soc. Japan* **48**, 791 (1928).

[34] L. Farkas, *Chem. Ber.* **90**, 2940 (1957).

[35] W. Baker and R. Robinson, *J. Chem. Soc.* 1985 (1925).

[36] S. Rangaswami and T. R. Seshadri, *Proc. Indian. Acad. Sci.* **10A**, 6 (1939).

[37] J. Allan and R. Robinson, *J. Chem. Soc.* 2192 (1924).

water (50 ml) added to the residue. The diketone (0·3 g) was filtered and it crystallized from benzene–light petroleum as small needles, m.p. 164–165°; it gave a red ferric reaction.

The above diketone (0·25 g) was heated at 100° with formic acid (15 ml) for 10 min. On dilution with water the product (0·1 g) was collected and crystallized from ethyl acetate, m.p. 246–247° alone or when mixed with bi(7-flavonyloxy)methane mentioned earlier; it gave a positive methylenedioxy test.

*Bi(2-hydroxy-deoxybenzoinyl-4-oxy)methane* (XI). 2,4-Dihydroxydeoxybenzoin (1 g) was refluxed in acetone solution (50 ml) with methylene iodide (0·2 ml) and $K_2CO_3$ (5 g) for 4 hr. The product (0·35 g) crsytallized from acetic acid as colourless clusters of prisms, m.p. 151–152°; it gave a red colour with ethanolic ferric chloride and a positive methylenedioxy test (Found: C, 74·3; H, 5·2; $C_{29}H_{24}O_6$ requires: C, 74·4; H, 5·1%).

*Reactions of* (XI)

(a) *With aluminium chloride.* The product (XI; 0·1 g) was heated in benzene solution (50 ml) with anhydrous $AlCl_3$ (2 g) for 24 hr. Benzene was distilled off and the complex decomposed with ice and HCl aq. After 24 hr at room temp, the mixture was extracted with ether and the ether solution extracted successively with 5% $NaHCO_3$ aq. and 5% $Na_2CO_3$ aq. The carbonate solution on acidification gave a solid which crystallized from ethyl acetate–light petroleum as colourless needles, m.p. 114–115° alone or when mixed with an authentic sample of 2,4-dihydroxyphenyl benzyl ketone.

(b) *With acetic anhydride–sodium acetate.* The compound (XI) (0·35 g) was refluxed with acetic anhydride (40 ml) and fused sodium acetate (4 g) at 180° for 30 hr. It was poured over ice and the product collected and crystallized from benzene and was obtained as colourless silky needles (0·1 g) m.p. 191–192° alone or when mixed with bi(2-methyl-7-isoflavonyloxy)methane (IVb), reported earlier. It gave a positive methylenedioxy test.

### *Inter-C-methylenation experiments*

(1) *Using resacetophenone* (VII)

*Bi-(2,4-dihydroxy-3-acetophenonyl)methane* (XII). Resacetophenone (5 g) was dissolved in ethanolic sodium ethoxide (4%, 50 ml) and treated with methylene iodide (2 ml) and left at room temp for 18 hr. It was heated at 60–70° for 1 hr and the solvent distilled off. Water (100 ml) was added to the residue and extracted with ether. The aqueous solution on acidification gave a solid (1 g) which crystallized from ethanol as colourless small prisms, m.p. 204–205°; it gave a red colour with ethanolic ferric chloride and a positive iodoform test and was soluble in $Na_2CO_3$aq.; $\lambda_{max}^{MeOH}$ 320, 284 m$\mu$ (log $\varepsilon$, 4·34, 4·43) [Found: C, 64·5; H, 5·2%; mol. wt. 308 (by cryoscopic method using benzene as the solvent). $C_{17}H_{16}O_6$ requires: C, 64·6; H, 5·1%, mol. wt. 316]. 2,4-Dinitrophenyl hydrazone crystallized from dioxane as orange crystals m.p. 285°(d).

*Reaction and derivatives of* (XII). (a) The product (XII; 0·2 g) was refluxed with $AlCl_3$ (1 g) in benzene solution (50 ml) for 24 hr. The product crystallized from ethanol as colourless small prisms, m.p. 204–205° alone or when mixed with the starting material.

(b) *Diacetate.* The compound (XII; 0·2 g) was suspended in acetic anhydride (10 ml) and a few drops of dry pyridine were added, shaken well until the solution was clear and then heated on a boiling water bath for 1 hr. On pouring the product over ice (200 g) a crystalline solid (0·15 g) separated which crystallized from ethyl acetate as colourless needles, m.p. 222°, (Found: C, 62·4; H, 5·0; $COCH_3$, 22·9; $C_{21}H_{20}O_8$ requires: C, 63·0; H, 5·0; $COCH_3$, 21·5%).

(c) *Tetra-acetate.* The bis-compound (XII; 0·5 g) was refluxed with acetic anhydride (15 ml) and pyridine (5–6 drops) for 2·5 hr. The tetra-acetate (0·5 g) crystallized from ethanol as colourless needles, m.p. 196° (Found: C, 61·5; H, 4.5; $COCH_3$, 37·1; $C_{25}H_{24}O_{10}$ requires: C, 62·0; H, 5·0; $COCH_3$, 35·5%).

(d) *Tetramethyl ether.* The product (XII: 0·5 g) in acetone solution (50 ml) was refluxed with dimethyl sulphate (1 ml) and $K_2CO_3$ (5 g) for 36 hr. Acetone was distilled off and water (100 ml) added to the residue. The solid was filtered, dried and taken up in benzene. The benzene solution was purified by chromatography over neutral alumina, using benzene as the eluting solvent. The eluent was concentrated and crystallized with the help of light petroleum when the tetramethyl ether (0·5 g) separated as colourless small needles, m.p. 109–110°; it gave a negative ferric reaction; $\lambda_{max}^{MeOH}$ 274 m$\mu$ (log $\varepsilon$, 4·42); $\nu_{max}^{KBr}$ 1660, 1584, 1570, 1273, 817 and 797 cm$^{-1}$) [Found: C, 67·4; H, 6·4.

$OCH_3$, 32·8; mol. wt. (by thermistor-drop method), 364, 376. $C_{21}H_{24}O_6$ requires: C, 67·7; H, 6·5; $OCH_3$, 33·3%; mol. wt. 372].

(e) *Bi-(7-hydroxy-8-flavonyl)methane* (XIII). The product (XII) (1 g) in acetone solution (100 ml) was refluxed with benzoyl chloride (2 ml) and $K_2CO_3$ (7 g) for 36 hr. Acetone was distilled off and the residue treated with water (125 ml). The solid was filtered, treated with 10% acetic acid to decompose the potassium salts and crystallized from benzene–light petroleum when the bis-diketonyl methane (0·75 g) separated as yellow prisms, m.p. 180–183°. The following analysis agrees with the requirements of a monobenzoate of bi(3,4-dihydroxy-3-dibenzoylmethanyl)methane; there seems to have been partial dibenzoylation. (Found: C, 74·4; H, 4·7; $C_{38}H_{28}O_9$ requires: C, 74·2; H, 4·5%). The product gave a positive ferric reaction and a copper complex with methanolic copper acetate.

The bis-diketonyl methane (0·1 g) was refluxed with 5% $K_2CO_3$ aq. and mixed with the above aqueous carbonate soluble portion and then saturated with carbon dioxide. The bisflavone (XIII 20 mg) crystallized from aqueous ethanol as colourless small prisms m.p. 300–301° (Found: C, 75·6; H, 4·6; $C_{31}H_{20}O_6$ requires: C, 76·2; H, 4·1%).

(2) *Using 2,4-dihydroxydeoxybenzoin* (X)

*Formation of bi-(2,4-dihydroxydeoxybenzoin-3-yl)methane* (XIV). 2,4-Dihydroxydeoxybenzoin (5 g) was reacted in ethanolic sodium ethoxide (3·3%, 60 ml) with methylene iodide (7 g) as in the case of resacetophenone. The resulting solution was cooled, diluted with water, acidified and filtered. The crude solid (3·5 g) crystallized from ethyl acetate–light petroleum as colourless clusters of prisms (1·5 g), m.p. 191–192° (Chakravarty *et al.*[31] report the same m.p.); it gave a red ferric reaction (Found: C, 74·5; H, 5·3, mol. wt. by Rast camphor method, 483; $C_{29}H_{24}O_6$ requires: C, 74·3; H, 5·2%, mol. wt. 468).

*Reaction and derivatives of* (XIV). (a) The compound (XIV; 0·1 g) was obtained unchanged after heating in benzene solution (35 ml) with $AlCl_3$ (0·5 g) for 24 hr.

(b) *Complete methyl ether.* The compound (XIV; 0·5 g) was refluxed in acetone solution (50 ml) with dimethyl sulphate (0·4 ml) and $K_2CO_3$ (4 g) for 36 hr. The product (0·5 g) crystallized from benzene–light petroleum as colourless small prisms, m.p. 114–115°; it gave a negative ferric reaction; $\lambda_{max}^{MeOH}$ 276 m$\mu$ (log $\varepsilon$, 4·33) (Found: C, 74·7; H, 5·9; $OCH_3$ 23·0; $C_{33}H_{32}O_6$ requires: C, 75·5; H, 6·2, $OCH_3$, 23·6%).

(c) *Diacetate.* Prepared by the pyridine–acetic anhydride method at 100°, crystallized from ethyl acetate as colourless needles, m.p. 218–219° (Found: C, 70·8; H, 5·1; $COCH_3$, 15·0; $C_{33}H_{28}O_8$ requires: C, 71·7; H, 5·1; $COCH_3$, 15·6%).

(d) *Tetra-acetate.* Prepared by refluxing with acetic anhydride and pyridine for 3 hr, crystallized from ethyl acetate–light petroleum as colourless small needles, m.p. 110–111° (Found: 68·9; H, 5·0; $C_{37}H_{32}O_{10}$ requires: C, 69·8; H, 5·0%).

(e) 2,4-*Dinitrophenylhydrazone.* Crystallized from ethanol as red coloured prisms m.p. 264–265°.

(f) *Bi(2-methyl-7-acetoxy-8-isoflavonyl)methane* (XVa). The bisdeoxybenzoinylmethane (0·35 g) was heated at 180–190° with acetic anhydride (50 ml) and sodium acetate (4 g) for 27 hr. The reaction mixture was poured over ice. The product (XVa; 0·25 g) crystallized from benzene as colourless small prisms, m.p. 254° (Found: C, 74·4; H, 4·9. $C_{37}H_{28}O_8$ requires: C, 74·0, H, 4·7%).

(g) *Bi(2-methyl-7-hydroxy-8-isoflavonyl)methane* (XVb). The above compound (XVa) was deacetylated using ethanolic hydrochloric acid, and the product (XVb) did not melt up to 360° (Found: C, 76·6; H, 4·9; $C_{33}H_{24}O_6$ requires: C, 76·7; H, 4·7%).

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*Note added in proof:* In a recent publication, D. Chakravarti and N. Chakravarti (*J. Ind. Chem. Soc.*, **40**, 957 (1963) have given a different bis structure for the methylenation product obtained from resacetophenone, methylene iodide and ethanolic potash. They have proposed a methylene link between the two w positions. This formulation is contradicted by (1) NMR spectral data, (2) positive iodoform reaction of the product and (3) lack of this methylenation when peonol is employed.