NUCLEAR METHYLATION OF CHALKONES AND FLAVANONES

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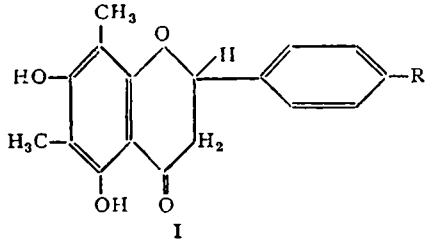
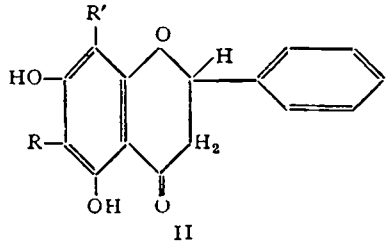
A number of flavanones with C-methyl groups are known to occur in Nature. They are matteucinol (I *a*), desmethoxy matteucinol (I *b*), farrerol (I *c*), strobopinin (II *a*) and cryptostrobin (II *b*). They have previously been synthesised by starting with nuclear methylated phloroglucinol.[1,2] They should also be capable of synthesis by direct nuclear methylation. With this object in view, a preliminary study (of simpler types) has now been made. When there is no hydroxyl in the 5-position of flavanones, the corresponding chalkones are more stable and could therefore be used for experiments on nuclear methylation. On the other hand when a 5-hydroxyl is present free, the flavanones themselves are quite stable and have to be subjected to nuclear methylation. Typical examples of these two types have now been examined under different conditions.



I

a, R = OCH_3; *b*, R = H; *c*, R = OH

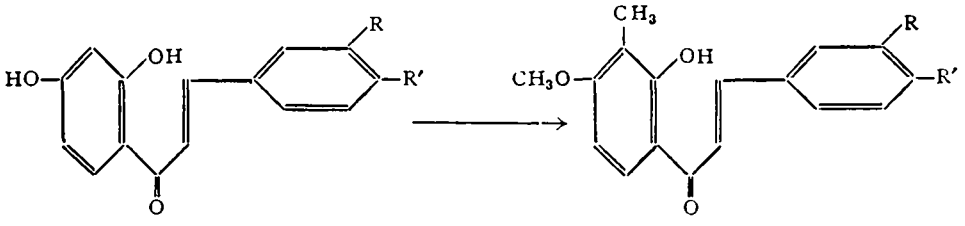


II

a, R = CH_3; R′ = H
b, R = H; R′ = CH_3

It has been earlier established that carbonyl derivatives of resorcinol, phloroglucinol and 5:7-dihydroxy flavonoids undergo ready C-methylation in the three and six positions respectively when treated with methyl iodide and methanolic alkali.[3] When the 2:4-dihydroxy-chalkones (III) are subjected to nuclear methylation, in all cases C-methylation takes place in the 3-position just as with the corresponding acetophenones. The exact constitution of the methylation products was established by comparing them with the synthetic samples (IV) obtained by the condensation of 2-hydroxy-3-methyl-4-methoxy acetophenone (V) with benzaldehyde, anisaldehyde and veratraldehyde respectively in the presence of alcoholic potash.

As a suitable example, 3-methyl-isoliquiritigenin-dimethyl ether (IV *b*) was heated with alcoholic sulphuric acid whereby it gave the corresponding flavanone, 8-methyl liquiritigenin-dimethyl ether (VI).

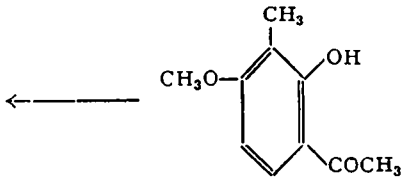


III

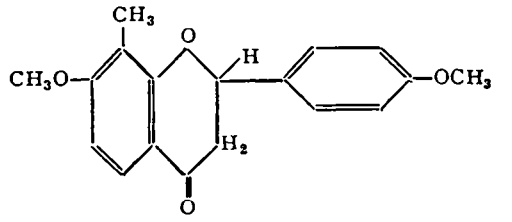
a, R = R′ = H
b, R′ = OH ; R = H
c, R = R′ = OCH_3

IV

a, R = R′ = H
b, R = H ; R′ = OCH_3
c, R = R′ = OCH_3

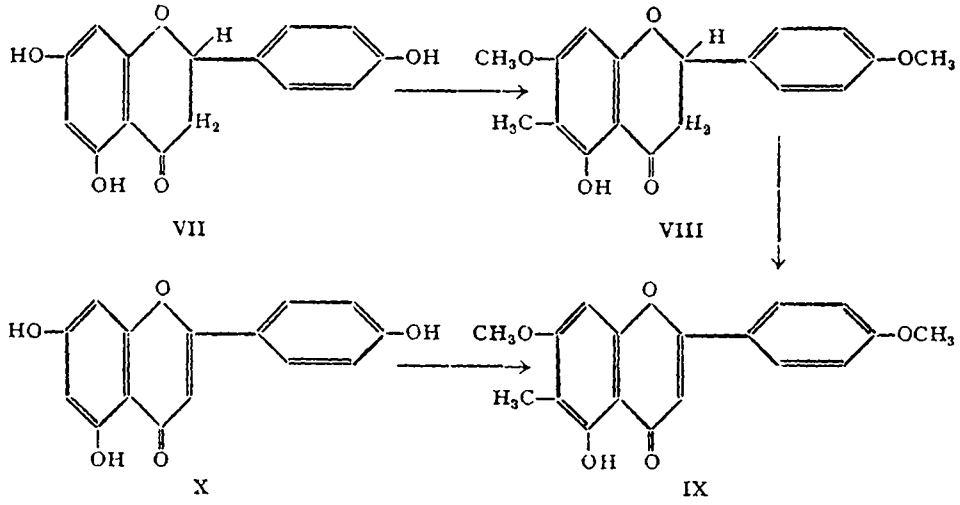


V



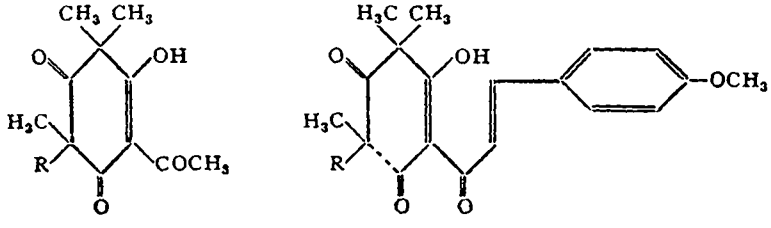
VI

Among flavanones, naringenin (VII) which is readily available has been used for two methods of nuclear methylation: (i) adding excess of methyl iodide first and then methanolic potash slowly during a period of three hours so as to avoid flavanone ring opening as far as possible: (ii) adding excess of methyl iodide and excess of methanolic alkali in one lot and then refluxing for three hours; this should lead to considerable ring opening. In both cases the product was taken up in ether and fractionated using extraction with aqueous sodium bicarbonate, sodium carbonate, aqueous sodium hydroxide, the remaining ether solution retaining the neutral fraction. In method (i) very little was obtained in earlier fractions and the major product was neutral. Though it gave ferric chloride colour, it was very sparingly soluble in alkali. The analytical values agreed with the requirements of 5-hydroxy-7 : 4′-dimethoxy-6-methyl flavanone (VIII). This constitution was confirmed by selenium dioxide oxidation to the corresponding flavone which was found to be identical with 5-hydroxy-7 : 4′-dimethoxy-6-methyl-flavone (IX) obtained by nuclear methylation of apigenin (X). Hence it could be concluded that when the flavanone ring is kept intact it undergoes nuclear methylation in the 6-position just as flavones and flavonols.



In method (ii), the sodium bicarbonate soluble fraction was found to agree with the C-trimethyl compound (XI *a*) and this was confirmed by synthesis using 5-acetyl-1 :3 :3-trimethyl-cyclohexen-(4)-*ol*-(4)-dione-(2 :6) (XI *a*) and anisaldehyde. The formation of the substance in the nuclear methylation could be attributed to the opening of the hetrocyclic ring in the presence of excess of alkali and subsequent nuclear methylation just as in the case of carbonyl derivatives of phloroglucinol.[4] The sodium carbonate fraction was found to be the C-tetramethyl compound (XII *b*) both from a study of its properties and also by its synthesis employing 5-acetyl-1 : 1 : 3 : 3-tetramethyl-cyclohexen-(4)-*ol*-(4)-dione-(2 : 6) (XI *b*) and anisaldehyde.

The sodium hydroxide fraction was a yellow crystalline solid, m.p. 156–57°, obtained in very poor yield. With alcoholic ferric chloride it gave brown colour. Because of small yield it was not further studied. The neutral fraction was found to be minor in quantity and was identified as 5-hydroxy-7 : 4′-dimethoxy-6-methyl flavanone (VIII) obtained conveniently by method (i).



a, R=H; *b*, R=CH_3

In connection with the identification of the nuclear methylated flavanone, the nuclear methylation of apigenin (X) has now been carried out using sodium methoxide and excess of methyl iodide. As in other cases it yields about 10% of the 6-methyl compound (IX) the constitution of which is derived from analogy with similar cases.[5] This comes as a neutral fraction. The aqueous sodium hydroxide soluble fraction is identical with apigenin-7:4′-dimethyl ether. There is a considerable amount of aqueous sodium carbonate soluble fraction which was found to be unchanged apigenin. There was no fraction extracted by sodium bicarbonate.

EXPERIMENTAL

2:4-*Dihydroxychalkone* (*III a*)

The method of preparation using alcoholic alkali for the condensation did not give a good yield of 2:4-dihydroxy chalkone[6] and hence the following method was employed: A steady current of dry hydrogen chloride gas was passed for three hours through an ice-cooled solution of resacetophenone dibenzoate (14 g.) and benzaldehyde (5 c.c.) in dry ethylacetate (200 c.c.). After leaving in the ice chest for twenty-four hours, ligroin was added in excess, when a dark red oil separated. This was washed with water, dissolved in alcohol and refluxed with aqueous potash (20 g. in 300 c.c.) for three hours. The product was cooled, acidified to Congo red and most of the alcohol removed by distillation under reduced pressure. The solid that separated was filtered, washed with boiling water, dried and crystallised twice from benzene yielding yellow needles (4 g.), m.p. 147–48° alone or when mixed with an authentic sample of 2:4-dihydroxy chalkone. It gave a dark reddish brown colour with alcoholic ferric chloride.

2-*Hydroxy*-3-*methyl*-4-*methoxychalkone* (*IV a*)

(i) *By chalkone condensation.*—Aqueous potassium hydroxide (3 g. in 3 c.c.) was added little by little to a solution of 2-hydroxy-3-methyl-4-methoxy-acetophenone[7] (1·8 g.) and benzaldehyde (1·1 c.c.) in alcohol (30 c.c.). The resulting solution after keeping tightly corked for twenty-four hours at room temperature, was diluted with water, cooled and acidified with dilute hydrochloric acid. The pale yellow precipitate was filtered, washed with sodium bicarbonate solution and crystallised from methyl alcohol when deep yellow rectangular rods and prisms (1·2 g.) were formed; m.p. 132–33° (Found: C, 75·3; H, 6·3; $C_{17}H_{16}O_3$ requires C, 76·1; H, 6·0%). It was sparingly soluble in aqueous sodium hydroxide and yielded a reddish brown colour with alcoholic ferric chloride.

(ii) *By nuclear methylation of* 2:4-*dihydroxychalkone* (*III a*).—A solution of chalkone (2 g.) in methanolic potash (2·5 g. in 25 c.c.) was cooled in ice, treated with methyl iodide (5 c.c.) and left in a well stoppered flask in an ice bath which was allowed to assume the laboratory temperature slowly. After keeping overnight, the resulting mixture was boiled under reflux for six hours with more of methyl iodide (2 c.c.). The alcohol was distilled off under vacuum, and the residue acidified and extracted with ether. The ether concentrate was dissolved in the minimum amount of methyl alcohol and the solution cooled. The sparingly soluble fraction was crystallised thrice from methanol when it formed deep yellow rectangular rods and prisms (0·5 g.) melting at 132–33° alone or when mixed with 2-hydroxy-3-methyl-4-methoxychalkone reported above.

The methanolic mother liquor yielded a product (1·2 g.) which crystallised from ethyl acetate-petroleum ether mixture as pale yellow needles melting at 105° alone or when mixed with an authentic sample of 2-hydroxy-4-methoxychalkone.[8]

2-*Hydroxy*-3-*methyl*-4:4′-*dimethoxychalkone* (*IV b*)

(i) *By chalkone condensation.*—2-Hydroxy-3-methyl-4-methoxyaceto-phenone (1·8 g.) and anisaldehyde (1·4 g.) were condensed with alcoholic potash (3 g. in 30 c.c.) in the same way as described earlier. The product crystallised from methyl alcohol as deep yellow rods (1·4 g.) melting at 145–46° (Found: C, 72·4; H, 6·5; $C_{18}H_{18}O_4$ requires C, 72·5; H, 6·1%). It was sparingly soluble in alkali, dissolved in concentrated sulphuric acid to an orange solution and yielded a reddish brown colour with alcoholic ferric chloride.

(ii) *By nuclear methylation.*—Isoliquiritigenin (III *b*) was prepared by a modification of the method of Nadkarni and Wheeler.[6] The crude product was taken up in ether and washed with limited quantities of aqueous sodium bicarbonate in order to remove *p*-hydroxybenzoic acid, washed with water and the ether solution evaporated. The chalkone is best crystallised from a large volume of benzene, m.p. 204–05°.

Isoliquiritigenin (III *b*) (2 g.) was methylated exactly in the same way as mentioned in the case of 2:4-dihydroxychalkone and the product fractionated using methyl alcohol. The sparingly soluble fraction, after two further crystallisations from methanol, yielded 2-hydroxy-3-methyl-4:4′-dimethoxychalkone as deep yellow rectangular rods and prisms (0·5 g.) m.p. 145–46° alone or when mixed with the sample obtained by synthesis. The methanolic mother liquor yielded 2-hydroxy-4:4′-dimethoxychalkone (1·3 g.) as yellow needles,[9] m.p. 113–14°.

3-*Methyl*-2 : 4 : 4′-*trimethoxychalkone*:

The samples of the above chalkone (0·5 g.) prepared by the two methods were separately heated with dimethyl sulphate (0·5 c.c.) and ignited potassium carbonate (2 g.) in acetone solution for 30 hours. The product was found to be the same, 3-methyl-2 : 4 : 4′-trimethoxy-chalkone crystallising from ethylacetate-petroleum ether mixture as colourless stout rectangular prisms, m.p. 103–04°. It gave no ferric reaction and formed an orange solution with concentrated sulphuric acid (Found: C, 73·2; H, 6·5; $C_{19}H_{20}O_4$ requires C, 73·1; H, 6·5%).

7 : 4′-*Dimethoxy*-8-*methyl-flavanone* [8-*Methyliquiritigenin dimethyl ether* (*VI*)]

2-Hydroxy-4 : 4′-dimethoxy-3-methylchalkone (IV *b*) (0·1 g.) was refluxed with 4% alcoholic sulphuric acid (50 c.c., containing 10 c.c. of water) for 48 hours. Alcohol was removed under reduced pressure and water was added to the residue. The solid that separated was filtered and fractionally crystallised (five times) from alcohol when colourless needles (10 mg.), m.p. 110–11° separated. It gave no colour with alcoholic ferric chloride.

2-*Hydroxy*-3-*methyl*-4 : 3′ : 4′-*trimethoxychalkone* (*IV c*)

(i) *By chalkone condensation.*—2-Hydroxy-3-methyl-4-methoxy-acetophenone (1·8 g.) and veratraldehyde (1·6 g.) were condensed with alcoholic potash and the product crystallised from methyl alcohol yielding deep yellow long prismatic rods, m.p. 163–64°. It was sparingly soluble in alkali, dissolved in concentrated sulphuric acid to an orange red solution and gave a brown colour with alcoholic ferric chloride (Found: C, 69·6; H, 6·3; $C_{19}H_{20}O_5$ requires C, 69·5; H, 6·1%).

(ii) *By nuclear methylation of butein*-3′ : 4′-*dimethyl ether* (*III c*).—Butein-3′ : 4′-dimethyl ether (III *c*) was obtained by the method of Mauthner[10] but it was found to melt at 202–03° after crystallisation from benzene. Mauthner reported the m.p. as 127–28°, while Goschke and Tambor[11] reported its m.p. as 203°.

The above chalkone (1·75 g.) was subjected to nuclear methylation as described earlier. The sparingly soluble fraction (0·55 g.) (methanol) had m.p. 163–64° alone or when mixed with 2-hydroxy-3-methyl-4 : 3′ : 4′-trimethoxy chalkone (IV *c*). The mother liquor yielded butein 4 : 3′ : 4′-trimethyl ether,[12] m.p. 156–58°.

3-*Methyl-butein-tetramethyl ether*

This was obtained by methylation of the above chalkone (IV *c*) with dimethyl sulphate and potassium carbonate. It crystallised from ethyl

acetate-petroleum ether mixture as colourless tiny prisms, m.p. 194–95° (Found: C, 70·7; H, 6·5; $C_{20}H_{22}O_5$ requires C, 70·2; H, 6·5%).

Nuclear methylation of naringenin (VII)

Method (I): (5-hydroxy-6-methyl-7: 4'-dimethoxy flavanone, VIII).—Naringenin (10 g.) was dissolved in anhydrous methanol (100 c.c.) and the solution refluxed with methyl iodide (30 c.c.) for three hours during which time methanolic potash (10 g./40 c.c.) was added in ten lots and more of methyl iodide (10 c.c.) was added during the reaction to compensate for loss by vapourisation. Excess of methyl iodide and methyl alcohol were distilled off under reduced pressure and water (500 c.c.) added. The solution was acidified with cold concentrated hydrochloric acid and extracted with ether. The ether solution was extracted with saturated aqueous sodium bicarbonate, 5% sodium carbonate and 4% sodium hydroxide. The extracts yielded no appreciable product on acidification. The remaining ether solution was washed with water three times, dried over anhydrous sodium sulphate, ether distilled off and the residue crystallised from methanol, yielding colourless needles, m.p. 148° (1 g.). It gave a bluish violet colour with alcoholic ferric chloride (Found: C, 68·4; H, 6·3; $C_{18}H_{18}O_5$ requires C, 68·8; H, 5·8%).

5-Hydroxy-7: 4'-dimethoxy-6-methyl flavone (IX)

(a) By selenium dioxide oxidation.—The above C-methyl-flavanone (VIII) (0·1 g.) was dissolved in acetic anhydride (6 c.c.), selenium dioxide (0·2 g.) added and the mixture heated under reflux at 140° for five hours. The mixture was filtered off and acetic anhydride removed under reduced pressure. Water was added to the residue and the solid that separated was filtered, washed with cold water and crystallised from methyl alcohol forming pale straw coloured needles (0·05 g.), m.p. 183–85° undepressed by the nuclear methylation product of apigenin (*see* below). It gave a green colour with alcoholic ferric chloride (Found: C, 68·7; H, 4·7; $C_{18}H_{16}O_5$ requires C, 69·2; H, 5·1%).

(b) By nuclear methylation of apigenin (X).—Apigenin (X) (2·7 g.), sodium methoxide from sodium (2·5 g.) and absolute methanol (50 c.c.) were employed following the method used earlier.[5] The method of working was, however, different and was as follows. The ether extract of the product was washed successively with saturated aqueous sodium bicarbonate (no extraction), 5% sodium carbonate (Fraction I) and 4% sodium hydroxide (Fraction II), the remaining ether solution contained neutral Fraction (III). Fraction (I) on acidification yielded a pale yellow compound, m.p. 343°

alone or mixed with apigenin. It gave a dark brown colour with alcoholic ferric chloride. Fraction (II) was acidified and the solid product crystallised from alcohol yielding a yellow compound, m.p. 270–71° undepressed by an authentic sample of apigenin-7 : 4′-dimethyl ether. It gave a dark brown colour with alcoholic ferric chloride. Neutral Fraction (III) on concentration gave a solid which crystallised from methanol as straw coloured needles, m.p. 183–85°, alone or admixed with the sample of (IX) obtained by selenium dioxide oxidation.

Method (II) (Polymethylated chalkones).—Naringenin (VII) (10 g.) was dissolved in dry methanol (100 c.c.) and methyl iodide (40 c.c.) and methanolic potash (10 g. in 40 c.c.) added all at once. The mixture was refluxed for three hours, excess of methyl iodide and methanol removed under reduced pressure and the residue treated with cold water (500 c.c.). The solution was acidified with cold concentrated hydrochloric acid and repeatedly extracted with ether. The ether solution was then successively extracted with saturated aqueous sodium bicarbonate (Fraction A), 5% sodium carbonate (Fraction B), 4% sodium hydroxide (Fraction C) and the remaining ether solution was then washed with water and dried over anhydrous sodium sulphate (neutral Fraction D).

Fraction A [5-(4′-*methyoxy-cinnamoyl*)-1 : 3 : 3-*trimethyl-cyclohexen*-(4)-ol-(4)-*dione*-(2 : 6)] (*XII a*):

The solution (200 c.c.) was acidified in the cold with concentrated hydrochloric acid. On keeping in the refrigerator overnight a yellow solid separated, which was filtered and crystallised from methanol yielding golden yellow rectangular tablets (3 g.), m.p. 177–78°, alone or when mixed with the synthetic sample described below. With alcoholic ferric chloride it gave a reddish brown colour and formed an organge yellow solution in concentrated sulphuric acid (Found: C, 69·7; H, 6·5; $C_{19}H_{21}O_5$ requires C, 69·5; H, 6·4%).

Synthesis.—5-Acetyl-1 : 3 : 3-trimethyl-cyclo-hexen-(4)-*ol*-(4)-dione-(2 : 6)[4] (XI *a*) (2·2 g.) and anisaldehyde (1·6 c.c., 1·1 mole) were dissolved in alcohol (200 c.c.) treated with aqueous caustic potash (12 g. in 10 c.c.) and kept at room temperature for forty-eight hours. It was then diluted with an equal volume of water and extracted with ether to remove excess of anisaldehyde. The aqueous solution was acidified under cooling with dilute hydrochloric acid. The mixture was extracted with ether, the extract dried over anhydrous sodium sulphate and evaporated. The residue crystallised from methanol as golden yellow rectangular tablets (0·55 g.), m.p. 177–78° undepressed by the above sample. The colour reactions were the same.

Fraction B [5-(4′-*methoxy-cinnamoyl*)-1 : 1 : 3 : 3-*tetra-methyl-cyclohexen*-(4)-ol-(4)-*dione*-(2 : 6)] (*XII b*):

The sodium carbonate extract was acidified with cold dilute hydrochloric acid and cooled in ice. The deep yellow solid product was filtered and crystallised from methanol to give yellow thin rectangular plates (3 g.), m.p. 108° alone or when mixed with a synthetic sample. It gave reddish brown colour with alcoholic ferric chloride and formed a yellow solution in concentrated sulphuric acid (Found: C, 69·2; H, 6·6; $C_{20}H_{22}O_5$ requires C, 69·7; H, 6·6%).

Synthesis.—5-Acetyl-1 :1 :3 :3-tetramethyl-cyclohexen-(4)-*ol*-(4)-dione-(2 :6)[4] (XI *b*), anisaldehyde (1·4 c.c., 1·1 mols) were condensed just as in the preparation of (XII *a*). The product crystallised from methanol to give deep yellow thin rectangular plates (0·8 g.), m.p. 108°. It gave a reddish brown colour with alcoholic ferric chloride and a yellow solution in concentrated sulphuric acid.

Neutral Fraction D [5-*Hydroxy*-6-*methyl*-7 : 4′-*dimethoxy flavanone* (*VIII*)]

The ether solution was distilled and the residue (0·2 g.) crystallised from methanol when colourless needles separated, m.p. 148° undepressed by the 5-hydroxy-6-methyl-7 : 4′-dimethoxyflavanone (VIII) sample obtained from the first method.

SUMMARY

Nuclear methylation of 2 : 4-dihydroxy-chalkones (III) give rise to 3-C-methyl derivatives just as in the case of resacetophenone. C-Methyl-chalkone-derivatives (IV) with substituents in the side phenyl nucleus have also been prepared by this method. For comparison, they have been synthesised using 3-methyl-peonol and appropriate derivatives of benzaldehyde. C-Methyl-*iso*-liquiritigenin-dimethyl-ether (IV *b*) was cyclised to the corresponding 8-methyl-flavanone (VI).

The flavanone, naringenin, when subjected to nuclear methylation under mild conditions yields 6-methyl-flavanone derivative (VIII) whereas under conditions in which the oxygen ring opens, beside the above 6-methyl flavanone (VIII), poly-C-methylated chalkones (XII *a* + *b*) are formed just as in case of phloracetophenone.

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