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EXPERIMENTS IN THE BRAZILANE SERIES—II
THE PREPARATION OF 6,5′,6′-TRIMETHOXYBRAZILANE

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Abstract—The synthesis of 6,5′,6′-trimethoxybrazilane from hydroquinone is described. In the course of this work, 6,5′,6′-trimethoxybrazylium ferrichloride was also synthesized and the reduction of related intermediate compounds with sodium and potassium borohydride was investigated.

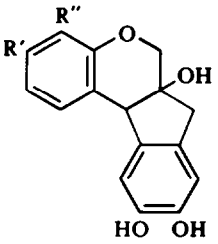
INTEREST in the chemistry of brazilin dates back to 1808 when Chevreul isolated the compound in a crystalline form.[1] The structural studies culminated with the postulation of its structure I[2] which was confirmed by synthesis.[3] So far the only other natural compound isolated having the brazilane structure (II) is haematoxylin (III). The nomenclature is in accordance to that adopted by Crabtree and Robinson.[4]

Crabtree and Robinson[5] synthesized the trimethyl ether of isobrazilein ferrichloride (IV), the ferrichloride salt of the trimethyl ether of brazilein.[6] The corresponding isohaematein salt was also synthesized. Thus these two compounds were the first two substances synthesized which possessed the brazilane skeleton.

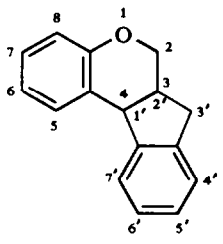
From their hydroxylation patterns, brazilin and haematoxylin appear to be related to the flavonoid substances[7] having a C_6—C_3—C_6 carbon skeleton. By analogy to the numerous flavonoid compounds known, other brazilane derivatives with variation in the positions of OH groups other than those at positions 7 and 8 might be expected to occur in nature, and in this paper the preparation, properties and derivatives of 6-methoxybrazilane is described.

Considering the biogenesis of brazilin and haematoxylin, Whalley[8] suggested that in accordance with the postulation that isoflavones arise from 2-phenyl-3-hydroxyflavans, 3-phenyl-4-hydroxyflavans by a Wagner-Meerwein 1:2 shift may be converted into 3-hydroxy-4-phenylflavans which may then condense with formaldehyde or its equivalent to yield the brazilane system. Representatives of the necessary intermediates were given as fustin (3,7,3′,4′-tetrahydroxyflavanone) and ψ-baptigenin (7-hydroxy-3′,4′-methylenedioxyisoflavone) and for brazilin and 8-methoxybutin (7,3′,4′-trihydroxy-8-methoxyflavanone) and melaccacidin (3,4,7,8,3′,4′-hexahydroxyflavan) for haematoxylin.

For the biogenesis of anthocyanins and anthoxanthins which also possess the C_6—C_3—C_6 carbon skeleton, Robinson[9] proposed the structure VIII as the common precursor. Besides the usual phloroglucinol orientation of the A-nucleus, the resorcinol arrangement is also found (butin, fiscetin, etc.) but less frequently. This nucleus often suffers further hydroxylation to yield compounds with OH groups at other possible positions of ring-A e.g. nobiletin (5,6,7,8,3′,4′-pentamethoxyflavone, baicalein (5,6,7-trihydroxyflavone).



I: R′ = OH, R″ = H
IIII: R′ = R″ = OH



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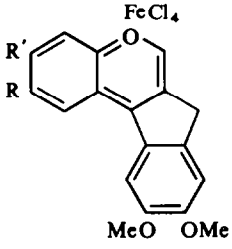

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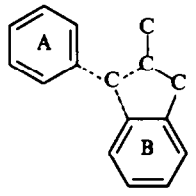

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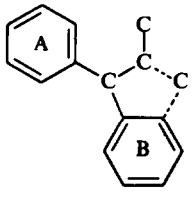

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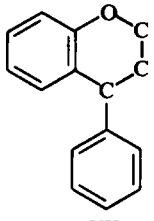

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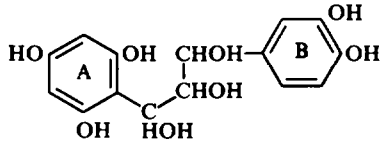

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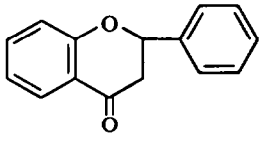

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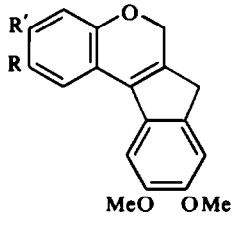
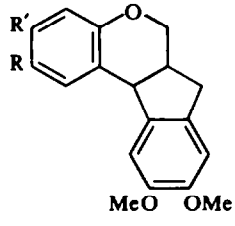


XI



XII

The phoroglucinol and resorcinol orientations of the A-nucleus are not characteristic of the B-nucleus where the commonest orientation of OH groups is the 3,4-dihydroxyphenyl arrangement, often O-methylated or methylenated. Changes in the hydroxylation pattern of ring-A have been illustrated by Seshadri[10]—the 5,7 dihydroxy derivatives seems to be the primary compounds, the 5,6,7 and 5,7,8-trihydroxybenzene structures involve a stage of oxidation and the 5,6,7,8-tetrahydroxybenzene nucleus results from a further stage of the same process. The 5,8 and 5,6-dihydroxy types seem to result from trihydroxy types by reduction with disappearance of the 7-hydroxyl. Similar reduction seems to produce fiscetion (3,7,3′,4′-

tetrahydroxyflavone and robinetin (3,7,3',4',5'-pentahydroxyflavone) in which the hydroxyl in the 5-position is lacking. Reduction at either position 5 or 7 is supported by evidence from the hydroxylation pattern of naturally occurring substances. However, there is no example of reduction at both these positions but it appears that if flavone IX isolated from the farina of *Primula pulverulenta*[11] and *P. japonica*, is derived from the fundamental precursor VIII, then at some stage in its formation, complete reduction of hydroxyls in rings-A and -B would have taken place. In the anthoxanthins, complete reduction in ring -B is represented by a large number of examples, e.g. chrysin (5,7-dihydroxyflavone), primetin (5,8-dihydroxyflavone) and baicalein (5,6,7-trihydroxyflavone), and it is not unlikely that the same may take place in ring -A. If this is acceptable, then reduction of hydroxyls at positions 5 and 7 of Xa to Xb may be conceded, the former obtained from the precursor VIII by nuclear oxidation at position 6 which is not without analogy to naturally occurring substances and to mild reactions in the laboratory.[12] These changes are shown in Fig. 1. In the conversion of Xa to Xb there is no particular analogy to show that position 6 should remain unchanged. It seems reasonable to suggest that a 6-hydroxybrazilane derivative could occur in nature and that it could arise from a C_6(A)—C_3—C_6(B) nucleus by an occasional synthesis under special circumstances, followed by condensation with a formaldehyde equivalent.

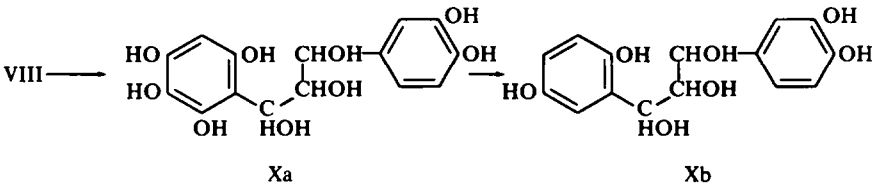


FIG. 1

p-Methoxyphenol prepared by semi-methylation of hydroquinone[13] was reacted with β-propiolactone to give β-(*p*-methoxyphenoxy)-propionic acid[14] the cyclization of which to 6-methoxychromanone was effected by an improved method using polyphosphoric acid. An intimate mixture of the finely powdered aryloxypropionic acid and polyphosphoric acid in the ratio of 1:20 by weight and maintaining the temperature of the reaction at 70° for one hour gave the best yield of 95%). Condensation of the chromanone with veratraldehyde in ethanolic hydrogen chloride solution, according to the method used by Perkin and Robinson[15] afforded 3-veratrylidene-6-methoxychromanone in almost quantitative yield. Analogous condensation of 6-methoxychromanone with benzaldehyde, anisaldehyde, 3-ethoxy-4-hydroxybenzaldehyde and 3-nitrobenzaldehyde resulted in very good yields of 3-benzylidene-6-methoxychromanone, 3-anisylidene-6-methoxychromanone, 3-(3'-ethoxy-4'-hydroxybenzylidene)-6-methoxychromanone and 3-(3'-nitrobenzylidene)-6-methoxychromanone respectively. Reduction of 3-veratrylidenechromanone could proceed in three stages, to yield, either a homoveratrylchromanone, a homoveratrylchromanol, a homoveratrylchroman or a mixture of these three. When hydrogenated at room temperature and atmospheric pressure in ethyl acetate solution catalysed by palladium on strontium carbonate (2%), 3-veratrylidene-6-methoxychromanone gave only one product, 3-homoveratryl-6-methoxychromanone in 83% yield.

Similar success was met with when 3-benzylidene, 3-anisylidene- and 3-(3'-ethoxy-4'-hydroxybenzylidene)-6-methoxychromanones were reduced under the same conditions, 3-Benzyl-6-methoxychromanone, 3-anisyl-6-methoxychromanone and 3-(3'-ethoxy-4'-hydroxybenzyl)-6-methoxychromanone were obtained in good yields varying from 60 to 85%.

The reduction of the 3-benzylidene and 3-benzyl-6-methoxychromanone derivatives with sodium and potassium borohydrides was investigated. The 4-ketonic group of the chromanone was reduced to the corresponding chromanol as expected, leaving the α,β-unsaturated linkage unaffected. Thus 3-benzylidene-6-methoxychromanol, 3-anisylidene-6-methoxychromanol and 3-veratrylidene-6-methoxychromanol were obtained from the corresponding chromanones. Similarly reduction with potassium borohydride of the dihydrochromanone derivatives afforded 3-homoveratryl-6-methoxychromanol, 3-benzyl-6-methoxychromanol and 3-anisyl-6-methoxychromanol.

The cyclodehydration of 7-methoxy-3-homoveratrylchromanone to deoxytrimethylbrazilone (XI R = H, R' = OMe) was accomplished by refluxing a benzene solution of the ketone in phosphoric anhydride.[16] Perkin and Robinson further reported that there were indications that 7-methoxy-3-homoveratrylchromanone was dehydrated by a variety of condensing agents, e.g. zinc chloride, stannic chloride, phosphoryl chloride, etc. but that the products were partly oxidized in acid solution to isobrazilein salts, the fluorescence of which was so characteristic. In the present experiments, 3-homoveratryl-6-methoxychromanone was effectively cyclodehydrated when treated with phosphoric anhydride in benzene, the required 6,5',6'-trimethoxybrazil-3-ene (XI, R = OMe, R' = H) being isolated. Its properties were similar to those of deoxytrimethylbrazilone, in that, it was easily oxidized in the presence of acids to isobrazilein salts. With concentrated sulphuric acid it gave a deep red colouration. Attempts to cyclize 3-homoveratryl-6-methoxychromanone with polyphosphoric acid, under various conditions did not meet with success. The required product could not be isolated, although the strong fluorescence of the aqueous solution indicated that cyclization and oxidation had occurred. A characteristic property of deoxytrimethylbrazilone (XI, R = H, R' = OMe) was the ease with which it was oxidized in acid solution with the formation of isobrazilein salts.[16] An analogous reaction of 6,5',6'-trimethoxybrazil-3-ene (XI, R = OMe, R' = H) with ferric chloride in acetic acid solution afforded beautiful crystals of 6,5',6'-trimethoxybrazylium ferrichloride (IV, R = OMe, R' = H). These crystals appeared brownish-red through transmitted light and exhibited blue reflex. In dilute solution of formic acid, greenish-yellow fluorescence appeared. Catalytic hydrogenation of O-diethylenedeoxyhaematoxylone to O-diethylenedeoxylane has been reported.[17] Similar hydrogenation of XI (R = OMe, R' = H) catalysed by palladium on strontium carbonate (2%) proceeded smoothly to yield 6,5',6'-trimethoxybrazilane in 73% yield.

EXPERIMENTAL

M.ps were determined on a hot stage microscope and are uncorrected. IR spectra were recorded on a Hilger and Watts H800. Elemental analysis were carried out by Dr. K. W. Zimmerman, Melbourne, Australia.

p-Methoxyphenol,[13] veratraldehyde[18] and β-(*p*-methoxyphenoxy)propionic acid[14] were prepared according to the methods described in the literature.

PPA cyclization of β-(p-methoxyphenoxy) propionic acid

6-Methoxychromanone. Finely powdered *β-(p*-methoxyphenoxy) propionic acid (0·5 g) was added to a mixture of phosphoric anhydride (7 g) and phosphoric acid (2 ml, S.G. 1·7). After 1 hr at 70°, the dark red complex was decomposed with ice–water. The solid which separated was filtered off and washed with dil $NaHCO_3$aq and water. The product was recrystallized from aqueous alcohol from which it separated in colourless needles (0·43 g, 95%) m.p. 47·5–50° (lit.[19] m.p. 49°).

3-Veratrylidene-6-methoxychromanone. A rapid stream of dry HCl was passed for approximately 20 min through a soln of 6-methoxychromanone (1 g) and veratraldehyde (1 g) in absolute alcohol (10 ml) kept at 0°. The passage of HCl was stopped when the soln assumed a dark red colour. The next day, the dark crystalline solid was isolated and crystallized from absolute alcohol. *3-Veratrylidene-6-methoxychromanone* was thus obtained as yellow rectangular plates, m.p. 157° (1·73 g, 94·5%), raised to 161° after 4 recrystallizations from the same solvent. (Found: C, 69·9; H, 5·7. $C_{19}H_{18}O_5$ requires: C, 69·9; H, 5·6%). With conc H_2SO_4 a purplish red soln was obtained.

3-Benzylidene-6-methoxychromanone. An ice-cold soln of freshly distilled benzaldehyde (1·2 g) and 6-methoxychromanone (2 g) in absolute alcohol (20 ml) was saturated with dry HCl. The passage of HCl was stopped when light brown crystals appeared. The next day, the ppt was collected, washed with water and crystallized. Four recrystallizations from absolute alcohol afforded 3-benzylidene-6-methoxychromanone as yellow needles, m.p. 120–122° (1·67 g, 68·1%). (Found: C, 76·4; H, 5·2. $C_{17}H_{14}O_3$ requires: C, 76·7; H, 5·3%). With conc H_2SO_4, a deep red coloration was produced.

3-Anisylidene-6-methoxychromanone. A soln of freshly distilled anisaldehyde (4·5 g) and 6-methoxychromanone (5 g) in absolute alcohol (30 ml) kept at approximately 0° was saturated with dry HCl. The next day, the ppt was collected and crystallized from absolute alcohol to give *3-anisylidene-6-methoxychromanone* in yellow irregular shaped prisms, m.p. 106–107° (7·2 g, 86·4%), raised to 108–109° after 3 recrystallizations from the same solvent. (Found: C, 73·1; H, 5·5. $C_{18}H_{16}O_4$ requires: 73·0; H, 5·4%).

3-(3'-Ethoxy-4'-hydroxybenzylidene)-6-methoxychromanone. A soln of 3-ethoxy-4-hydroxybenzaldehyde (1 g) and 6-methoxychromanone (1 g) in absolute alcohol (20 ml) was cooled with an ice-bath and saturated with dry HCl. The passage of HCl was stopped when the soln turned red and a ppt appeared. The next day, the solid was filtered off and crystallized from absolute alcohol. *3-(3'-Ethoxy-4'-hydroxybenzylidene)-6-methoxychromanone* separated in the form of yellow rhombic crystals, m.p. 166–170°. (1·5 g, 81·9%), raised to 170–172° after 3 recrystallizations from the same solvent. (Found: C, 69·5; H, 5·6. $C_{19}H_{18}O_5$ requires: C, 69·9; H, 5·6%).

3-(3'-Nitrobenzylidene)-6-methoxychromanone. A stream of dry HCl was passed for approximately 15 min through a soln of 6-methoxychromanone (50 mg) and *m*-nitrobenzaldehyde (50 mg) in absolute alcohol (5 ml). The passage of HCl was stopped when the soln turned red in colour. The next day, the soln was diluted with water and the ppt was filtered off and crystallized from absolute alcohol. The crystals of *3-(3'-nitrobenzylidene)-6-methoxychromanone* were in the form of short yellow needles, m.p. 153–155° (40 mg), raised to 160–161·5° by 3 recrystallizations from the same solvent. (Found: C, 65·5; H, 4·2. $C_{17}H_{13}NO_5$ requires: C, 65·6; H, 4·2%).

3-Homoveratryl-6-methoxychromanone. Pd on $SrCO_3$ (2%) was added to 3-veratrylidene-6-methoxychromanone (1 g) dissolved in EtOAc (100 ml) and the yellowish soln hydrogenated at room temp and atmospheric press. After less than ½ hr slightly more than the theoretical quantity of H_2 was taken up. The colourless soln was filtered from the catalyst, and on concentration yielded a viscous oil which crystallized from absolute alcohol to give *3-homoveratryl-6-methoxychromanone* as colourless plates, m.p. 120–121° (0·83 g, 82·6%), raised to 123–124° after 3 recrystallizations from the same solvent; λ_{max} 6·0 μ (>C=O) (Found: C, 69·3; H. 6·1. $C_{19}H_{20}O_5$ requires: C, 69·5; H, 6·1%). With conc H_2SO_4 it gave a pale yellow solution.

3-Benzyl-6-methoxychromanone. A soln of 3-benzylidene-6-methoxychromanone (1 g) in EtOAc (100 ml) was hydrogenated at room temp and atmospheric press with Pd on $SrCO_3$ (2%) as a catalyst. After 16 min, slightly more than the theoretical quantity of H_2 was absorbed. On filtration and concentration, a viscous oil was obtained which crystallized from absolute alcohol to give *3-benzyl-6-methoxychromanone* as colourless rhombic plates, m.p. 72–74° (0·73 g, 73·9%), raised to 74–75° by three further recrystallizations from the same solvent; λ_{max} 6·0 μ (>C=O) (Found: C, 76·2; H, 6·0. $C_{17}H_{16}O_3$ requires: C, 76·1; H, 6·0%). The substance dissolved in conc H_2SO_4 to give a light yellow soln, from which on dilution with water, a clear soln resulted.

3-Anisyl-6-methoxychromanone. 3-Anisylidene-6-methoxychromanone (2 g) dissolved in EtOAc (100 ml), was catalytically reduced at room temp and atmospheric press, using Pd on $SrCO_3$ (2%) as a catalyst. In less than 1 hr, slightly more than the theoretical quantity of H_2 (210 ml) was taken up. On filtration and concentration *3-anisyl-6-methoxychromanone* was obtained. It crystallized from absolute alcohol as colourless plates, m.p. 94–96° (1·6 g, 79·4%), raised to 99–100° after 3 recrystallizations from the same solvent; λ_{max} 6·0 μ (>C=O). (Found: C, 72·9; H, 6·1. $C_{18}H_{18}O_4$ requires: C, 72·5; H, 6·1%). With conc H_2SO_4 an orange solution was obtained.

3-(3'-Ethoxy-4'-hydroxybenzyl)-6-methoxychromanone. Hydrogenation of 3-(3'-ethoxy-4'-hydroxybenzylidene)-6-methoxychromanone (1 g) in EtOAc under the usual conditions with Pd on $SrCO_3$ (2%) afforded *3-(3'-ethoxy-4'-hydroxybenzyl)-6-methoxychromanone*, m.p. 137–139° (0·6 g). After 4 recrystallizations from absolute alcohol, it separated as yellow prisms, m.p. 139–141°; λ_{max} 6·0 μ (>C=O). (Found: C, 69·6; H, 6·1. $C_{19}H_{20}O_5$ requires: C, 69·5; H, 6·1%). With conc H_2SO_4, it gave a light coloration while the unreduced substance gave a deep purplish red colour.

6,5',6'-Trimethoxybrazil-3-ene. Phosphoric anhydride (26 g) was added in three lots at ½ hr intervals to a soln of 3-homoveratryl-6-methoxychromanone (2 g) in benzene (80 ml) heated under reflux and protected with a $CaCl_2$ tube. Heating was continued for another hr.

The benzene layer was poured off and the dark complex after having been cooled, was broken up with crushed ice. The aqueous soln was extracted with ether and dried over K_2CO_3. The removal of the solvent afforded a reddish oil which crystallized from benzene–alcohol to give *6,5',6'-trimethoxybrazil-3-ene* as colourless fine needles (0·37 g), m.p. 122–126° (dec), raised to 126–128° after 3 recrystallizations from the same solvents. (Found: C, 73·0; H, 6·1. $C_{19}H_{18}O_4$ requires: C, 73·5; H, 5·9%). The substance dissolved in conc H_2SO_4 to give a deep red soln, from which on dilution with water, a brownish ppt of the pyrylium sulphate salt separated.

6,5',6'-Trimethoxybrazylium ferrichloride. The trimethoxybrazil-3-ene (0·1 g) was dissolved in slightly warm AcOH (8 ml) and anhydrous $FeCl_3$ added in lots until no more dissolved. The next day, a solid was collected and crystallized from formic acid. *6,5',6'-Trimethoxybrazylium ferrichloride* separated in the form of rod-shaped crystals, m.p. 206–208°, raised to 209–210° after 2 recrystallizations from the same solvent. (Found: C, 45·1; H, 3·4. $C_{19}H_{17}Cl_4FeO$ requires: C, 45·0; H, 3·4%).

6,5',6'-Trimethoxybrazilane. Pd on $SrCO_3$ (2%) was added to the trimethoxybrazilene (150 mg) dissolved in EtOAc (25 ml) and the soln hydrogenated at room temp and atmospheric press. After 42 min, no more absorption occurred. On filtration and concentration, *6,5',6'-trimethoxybrazilane* was obtained. It crystallized to 108° after 3 recrystallizations from the same solvent. (Found: C, 73·4; H, 6·4. $C_{19}H_{20}O_4$ requires: C, 73·1; H, 6·5%). With conc H_2SO_4 a slightly pinkish soln was obtained.

Reduction of 3-benzylidene-, 3-anisylidene- and 3-veratrylidene-6-methoxychromanone

3-Benzylidene-6-methoxychromanol. K_4BH_4 (0·5 g) was added in very small lots to 3-benzylidene-6-methoxychromanone dissolved in boiling MeOH (20 ml). After a further 10 min heating under reflux, the soln was concentrated. On the addition of a little water and on cooling, *3-benzylidene-6-methoxychromanol* was obtained (0·5 g). The analytical sample was recrystallized 4 times from absolute alcohol as colourless needles, m.p. 124–126°; λ_{max} 3·1 μ (—OH); λ_{max} 6·0 μ (>C=O) absent. (Found: C, 75·9; H, 6·2. $C_{17}H_{16}O_3$ requires: C, 76·1; H, 6·0%). With conc H_2SO_4 a greenish soln was obtained which gradually turned to reddish brown.

Similarly *3-anisylidene-6-methoxychromanol* was obtained from 3-anisylidene-6-methoxychromanone. It was recrystallized from absolute alcohol as colourless needles, m.p. 111–112°; λ_{max} 3·1 μ (—OH); λ_{max} 6·0 μ (>C=O) absent. (Found: C, 72·2; H, 6·2. $C_{18}H_{18}O_4$ requires: C, 72·5; H, 6·1%).

Similarly *3-veratrylidene-6-methoxychromanol* was obtained from 3-veratrylidene-6-methoxychromanone. After 4 recrystallizations from absolute alcohol, it separated as colourless needles, m.p. 144–146°; λ_{max} 2·9 μ (—OH). (Found: C, 69·4; H, 6·2. $C_{19}H_{20}O_5$ requires: C, 69·5; H, 6·1%). With conc H_2SO_4 it gave a transient green coloration.

Reduction of 3-homoveratryl-, 3-benzyl- and 3-anisyl-6-methoxychromanone

3-Homoveratryl-6-methoxychromanol. Reduction of 3-homoveratryl-6-methoxychromanone (0·5 g) dissolved in boiling MeOH (35 ml) with KBH_4 (0·5 g) afforded *3-homoveratryl-⁶-methoxychromanol.* It

crystallized from MeOH in short colourless needles, m.p. 152–154° (0·48 g), raised to 160–163° after 4 recrystallizations from the same solvent; λ_{max} 2·9 μ (—OH); λ_{max} 6·0 μ (>C=O) absent. (Found: C, 68·9; H, 6·6. $C_{19}H_{22}O_5$ requires: C, 69·0; H, 6·7%).

3-Benzyl-6-methoxychromanol. Following the procedure for the reduction of chromanone derivatives with KBH_4, $NaBH_4$ (0·3 g) was added in very small portions to 3-benzyl-6-methoxychromanone (0·3 g) dissolved in boiling MeOH. After heating under reflux, for a further 10 min, the soln was concentrated. On the addition of a little water and on cooling, *3-benzyl-6-methoxychromanol* separated in long colourless needles, m.p. 117–118° (0·3 g), raised to 119–121° after 3 recrystallizations from aqueous alcohol; λ_{max} 3·0 μ (—OH); λ_{max} 6·0 μ (>C=O) absent. (Found: C, 75·4; H, 6·7. $C_{17}H_{18}O_3$ requires: C, 75·5; H, 6·7%). With conc H_2SO_4, a pale yellow soln was obtained.

3-Anisyl-6-methoxychromanol. Similar $NaBH_4$ reduction of 3-anisyl-6-methoxychromanone gave the corresponding alcohol which recrystallized from aqueous MeOH in short needles, m.p. 121–125°; λ_{max} 3·0 μ (—OH); λ_{max} 6·0 μ (>C=O) absent. (Found: C, 72·3; H, 6·8. $C_{18}H_{20}O_4$ requires: C, 72·0; H, 6·7%).

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