

Application of a Lanthanide Shift Reagent, $\text{Eu}(\text{fod})_3$, to the Elucidation of the Structures of Flavones and Related Compounds

By Masayoshi Okigawa, Nizam U. Khan, and Nobusuke Kawano,* Faculty of Pharmaceutical Sciences, Nagasaki University, Nagasaki, Japan 852
Wasiur Rahman, Chemistry Department, Aligarh Muslim University, Aligarh, India

Application of the paramagnetic shift reagent $\text{Eu}(\text{fod})_3$ in n.m.r. spectral studies of 5,7-dimethoxyflavone derivatives showed that the signals due to H-3, H-6, and H-8 could be distinguished on the basis of lanthanide-induced shifts; the method is thus useful for structural assignments and has been successfully applied to methyl ethers of biflavones, isoflavones, and xanthenes. The difference in co-ordination state between $\text{Eu}(\text{fod})_3$ and $\text{Eu}(\text{dpm})_3$ in the case of 5-methoxychromone derivatives is discussed.

IN elucidation of the structures of new flavones and related compounds the position of substituents is not easy to decide; in particular the positions of internuclear linkages in biflavones are not always readily determined. For example, natural hinokiflavone (1) was initially considered to have a 4'-O-8'' linkage (2)¹ on the basis of a positive Gibbs reaction of the degradation product (3) of the penta-O-methyl derivative (4). Nakazawa² synthesized the 4'-O-6''- and 4'-O-8''-linked penta-O-methylbiapigenyl ethers (4) and (5); the former (4) was identical with the naturally derived penta-O-methylhinokiflavone. The Gibbs test³ should be used with great caution as it may lead to erroneous conclusions. The application of solvent-induced shifts⁴ in n.m.r. spectroscopy is useful for assigning the positions of aromatic methoxy-groups; Pelter has used this method for the elucidation of the structures of hexa-O-methylagathisflavone (6)⁵ and the two methyl ethers (4) and (5).⁶ However, in the case of hepta-O-methylsaharanflavone (7),⁷ one methoxy-signal (τ 6.56) moves hardly at all on addition of C_6D_6 , supporting a 3,6''-linked structure, contrary to the 3,8''-linkage which was later confirmed by synthetic studies.⁸ This anomaly restricts the use of benzene-induced shifts for deciding the location of a flavone-flavone linkage. We describe here a method of solving such structural problems in flavones and related compounds by using a shift reagent, $\text{Eu}(\text{fod})_3$ [tris-(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-octane-4,6-dionato)europium(III)].

Monoflavones.—For tri-O-methylapigenin (8), tetra-O-methylscutellarein (9), tetra-O-methylscutellarein (10), and ponkanetin (11) the magnitudes of lanthanide-induced shifts (Δ_{Eu}) were estimated (Table 1).⁹ Although gradients of shift *vs.* molar ratio curves (*S* values) were used in ref. 10, these are sometimes incon-

venient to estimate because considerable curvature was often observed, especially in the case of $\text{Eu}(\text{dpm})_3$ [tris-(2,2,6,6-tetramethylheptane-3,5-dionato)europium(III)]. Of the three reagents shown in Table 1, $\text{Eu}(\text{fod})_3$ is most effective for methoxy-protons at the 5-position (MeO-5) and the best reagent for distinguishing H-3, -6, and -8 from each other by means of Δ_{Eu} values. The Δ_{Eu} values of H-6 or MeO-6 are much larger than those of H-8 or MeO-8, providing a method of distinguishing a proton attached to either C-6 or C-8. $\text{Eu}(\text{dpm})_3$ is less effective for MeO-5 and gives comparatively similar values for other protons except those on the phenyl ring. The shift effects of $\text{Eu}(\text{fhd})_3$ [tris-(1,1,1-trifluoro-5,5-dimethylhexane-2,4-dionato)europium(III)]¹¹ seem to be smaller than those of $\text{Eu}(\text{fod})_3$. Therefore, $\text{Eu}(\text{fod})_3$ was used in the present studies.

The effect of $\text{Eu}(\text{fod})_3$ on H-3 is markedly different from that of $\text{Eu}(\text{dpm})_3$, especially in the cases of tetra-O-methylscutellarein (10) and ponkanetin (11), which have a 6- as well as a 5-methoxy-group. For compounds (10) and (11) the H-3 signal shows an upfield shift on addition of $\text{Eu}(\text{fod})_3$ and a downfield shift with $\text{Eu}(\text{dpm})_3$; the other two compounds [(8) and (9)] show little shift with $\text{Eu}(\text{fod})_3$ and relatively large downfield shifts with $\text{Eu}(\text{dpm})_3$.

Definitive assignment of every proton signal of flavones is usually not easy although Massicot¹² and Williams^{4,13} have reported work in this area. If ring A of the flavone nucleus has only one aromatic proton, it is especially difficult to distinguish its signal from that of H-3 and to define its position. The full assignment of every methoxy signal is also difficult when the flavone compound has many methoxy groups.

The assignments shown in Table 1 were confirmed by other methods as follows: (a) benzene-induced shift studies on tetra-O-methylscutellarein (10) showed small

¹ Y. Fukui and N. Kawano, *J. Amer. Chem. Soc.*, 1959, **81**, 6331.

² K. Nakazawa, *Chem. and Pharm. Bull. (Japan)*, 1968, **16**, 2503.

³ H. Schmid, A. Ebnöther, and M. Burger, *Helv. Chim. Acta*, 1950, **33**, 609; H. Inouye, Y. Kanaya, and Y. Murata, *Chem. and Pharm. Bull. (Japan)*, 1959, **7**, 573.

⁴ R. G. Wilson, J. H. Bowie, and D. H. Williams, *Tetrahedron*, 1968, **24**, 1407.

⁵ A. Pelter, R. Warren, J. N. Usmani, R. H. Rizvi, M. Ilyas, and W. Rahman, *Experientia*, 1969, **25**, 351.

⁶ A. Pelter, R. Warren, J. N. Usmani, M. Ilyas, and W. Rahman, *Tetrahedron Letters*, 1969, 4259.

⁷ A. Pelter, R. Warren, K. K. Chexal, B. K. Handa, and W. Rahman, *Tetrahedron*, 1971, **27**, 1625, 3724.

⁸ Y. Ikeshiro and M. Konoshima, *Tetrahedron Letters*, 1972, 4383.

⁹ M. Okigawa and N. Kawano, *Chem. and Ind.*, 1973, 850.

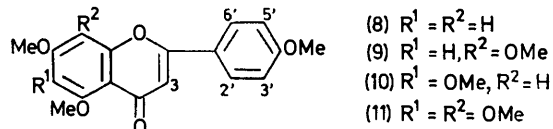
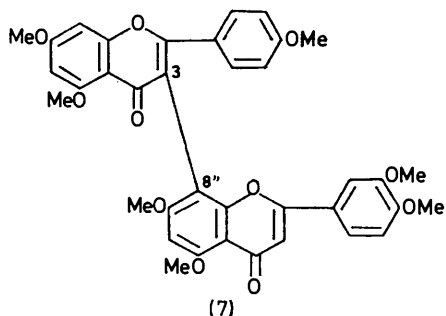
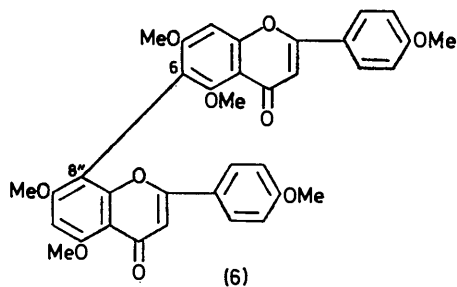
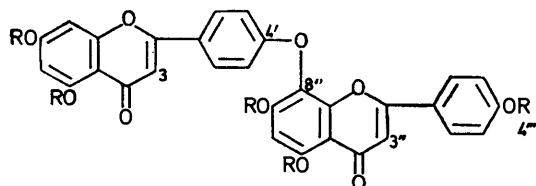
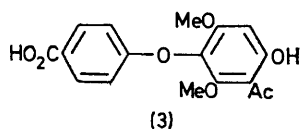
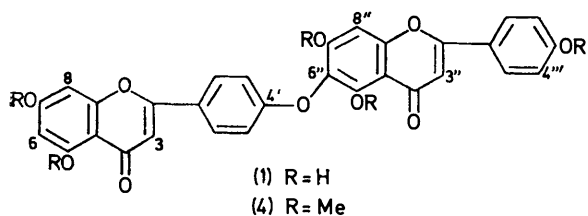
¹⁰ M. Okigawa, N. Kawano, W. Rahman, and M. M. Dhar, *Tetrahedron Letters*, 1972, 4125.

¹¹ H. E. Francis and W. F. Wagner, *Org. Magnetic Resonance*, 1972, **4**, 189; J. K. M. Sanders, S. W. Hanson, and D. H. Williams, *J. Amer. Chem. Soc.*, 1972, **94**, 5325.

¹² J. Massicot, J. P. Marthe, and S. Heitz, *Bull. Soc. chim. France*, 1963, 2712; D. Anker, C. Mercier, M. Baran-Marszak, and J. Massicot, *Tetrahedron*, 1969, **25**, 5027.

¹³ R. G. Wilson and D. H. Williams, *J. Chem. Soc. (C)*, 1968, 2477.

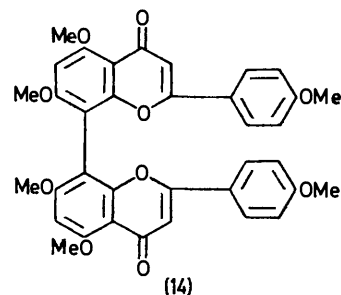
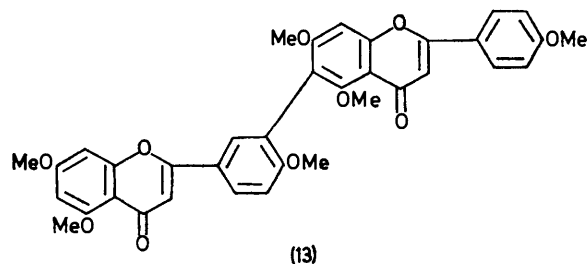
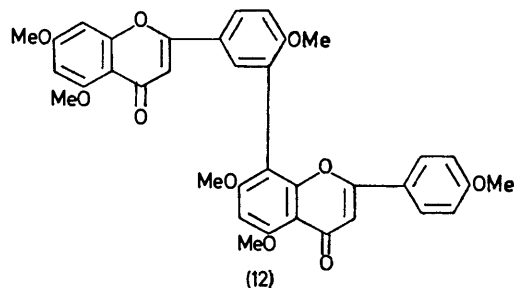
shifts (0.05 and 0.11 p.p.m.) of methoxy-signals at δ 3.97 (MeO-5) and 3.90 (MeO-6) and the usual high-field shifts (0.71 and 0.62 p.p.m.) of the other two



methoxy signals at δ 3.97 (MeO-7) and 3.88 (MeO-4'); (b) in nuclear Overhauser effect (n.O.e.) studies of the same compound (10) the singlet at δ 6.79 (H-8) showed 32% enhancement on irradiation at δ 3.97, and irradi-

¹⁴ A. K. Varshney, W. Rahman, M. Okigawa, and N. Kawano, *Experientia*, 1973, **29**, 784.

ation at δ 3.88 caused 17% enhancement of the two-proton doublet at δ 7.00 (H-3' and -5'); (c) the methoxy-signal at δ 3.92 (MeO-8) of tetra-*O*-methylisoscutearein (9) showed little shift (0.15 p.p.m.) in benzene-induced shift studies, whereas the other three methoxy-groups showed high-field shifts [0.45 (MeO-5), 0.73 (MeO-7), and 0.66 p.p.m. (MeO-4')]; and (d) 36% enhancement of a one-proton signal at δ 6.44 (H-6) of compound (9) was



observed when the methoxy-signal at δ 3.96 was irradiated, and 15% enhancement of the two-proton doublet at δ 7.02 (H-3' and -5') was observed when the methoxy-signal at δ 3.85 was irradiated. These results all conform with those obtained by lanthanide-induced shift studies.

Biflavones.—The following seven biflavone methyl ethers were studied: hexa-*O*-methylamentoflavone (12), hexa-*O*-methylrobustaflavone (13),¹⁴ hexa-*O*-methylcupressuflavone (14),¹⁵ hexa-*O*-methylagathisflavone (6),⁵ hepta-*O*-methylsaharanflavone (7),⁷ penta-*O*-methylhinokiflavone (4), and the 4'-*O*-8''-linked compound (5). Table 2 shows the *S* values of every proton signal of these compounds obtained on addition of Eu(fod)₃, which gives a straight line up to a 1 : 1 molar ratio of reagent to substrate. Therefore, in these cases *S* values are the same as Δ_{Eu} values. The same induced-shift bends were observed as in the case of the four compounds in Table 1, although the effectiveness of the

¹⁵ V. V. S. Murti, P. V. Raman, and T. S. Seshadri, *Tetrahedron*, 1967, **23**, 379.

added $\text{Eu}(\text{fod})_3$ is halved owing to the presence of two flavone nuclei per molecule. However, MeO-5 and -5'' (6), (7), and (4)] in comparison with compounds (12) and (5).

TABLE 1
 δ Values (from Me_4Si) and europium-induced shifts (Δ_{Eu} values)

| Compound | Protons | δ | Δ_{Eu} (p.p.m.) | | |
|----------|---------|----------------------|-------------------------------|---------------------------|---------------------------|
| | | | $\text{Eu}(\text{fod})_3$ | $\text{Eu}(\text{fhd})_3$ | $\text{Eu}(\text{dpm})_3$ |
| (8) | MeO-5 | 3.92 | 13.37 | 8.22 | 4.96 |
| | -7 | 3.87 | 1.06 | 0.95 | 1.04 |
| | -4' | 3.84 | 0 | 0.04 | 0.12 |
| | H-3 | 6.56 (s) | 0.04 | 0.90 * | 3.68 |
| | -6 | 6.34 (d, J 2 Hz) | 5.94 | 4.39 | 3.65 |
| | -8 | 6.53 (d, J 2 Hz) | 1.51 | 1.44 | 1.92 |
| | -2',6' | 7.79 (d, J 9 Hz) | 0 | 0.40 | 0.64 |
| | -3',5' | 6.97 (d, J 9 Hz) | 0 | 0.11 | 0.25 |
| | (9) | MeO-5 | 3.96 | 15.29 | 9.34 |
| -7 | | 3.98 | 1.93 | 1.39 | 1.48 |
| -8 | | 3.92 | 0.58 | 0.58 | 2.12 |
| -4' | | 3.85 | -0.07 | 0.03 | 0.15 |
| H-3 | | 6.60 (s) | -0.30 | 0.38 * | 4.35 |
| -6 | | 6.44 (s) | 7.48 | 5.08 | 5.36 |
| -2',6' | | 7.90 (d, J 9 Hz) | -0.12 | 0.28 | 0.74 |
| -3',5' | | 7.02 (d, J 9 Hz) | -0.09 | 0.02 | 0.02 |
| (10) | | MeO-5 | 3.97 | 11.83 | 11.47 |
| | -6 | 3.90 | 5.35 | 4.47 | 3.84 |
| | -7 | 3.97 | 1.12 | 0.90 | 1.45 |
| | -4' | 3.88 | -0.20 | -0.13 | -0.05 |
| | H-3 | 6.59 (s) | -1.50 | -0.84 | 2.04 |
| | -8 | 6.79 (s) | 1.20 | 1.15 | 3.10 |
| | -2',6' | 7.84 (d, J 9.5 Hz) | -0.49 | -0.43 | -0.24 |
| | -3',5' | 7.00 (d, J 9.5 Hz) | -0.25 | -0.22 | -0.25 |
| | (11) | MeO-5 | 3.95 | 13.23 | 13.68 |
| -6 | | 3.95 | 6.42 | 6.68 | 2.30 |
| -7 | | 4.09 | 1.66 | 1.58 | 1.66 |
| -8 | | 4.02 | 0.38 | 0.32 | 1.29 |
| -4' | | 3.88 | -0.17 | -0.12 | -0.19 |
| H-3 | | 6.60 (s) | -1.99 | -1.30 | 1.79 |
| -2',6' | | 7.87 (d, J 9.5 Hz) | -0.66 | -0.55 | -0.25 |
| -3',5' | | 7.01 (d, J 9.5 Hz) | -0.30 | -0.30 | -0.24 |

* Difficult to estimate owing to signal broadening. Minus signs indicate upfield shifts: $\Delta_{\text{Eu}} = \delta_{\text{Eu}}^{n-1} - \delta_{\text{Eu}}^{n=0}$ (CDCl_3), where n is the molar ratio of shift reagent to solute

TABLE 2
 S Values of fully methylated biflavones with $\text{Eu}(\text{fod})_3$

| Protons | Compounds | | | | | | |
|---------|-----------|--------|-------|-------|---------|---------|---------|
| | (12) | (13) | (14) | (6) | (7) | (4) | (5) |
| MeO-5 | 6.12 | 10.58 | 7.34 | 2.14 | 5.13 | 10.02 | {6.88} |
| -5'' | 8.78 | 2.64 | | 11.16 | 11.90 | 4.38 | {6.60} |
| -7 | 0.36 | {0.74} | 0.72 | 0.44 | 0.46 | 0.80 | {0.82} |
| -7'' | 1.06 | {0.56} | | 2.04 | 2.50 | 0.58 | {0.52} |
| -4' | 0.12 | {0.32} | -0.06 | 0.02 | -0.50 | | |
| -4''' | -0.08 | -0.06 | | -0.08 | 0 * | -0.06 | -0.10 |
| H-3 | {0.02} | {0.30} | 0.18 | 0.06 | | {0.36} | {0.14} |
| -3'' | {-0.16} | {0.16} | | 0.28 | -0.44 | {-0.06} | {0.26} |
| -6 | 2.76 | 4.84 | 3.66 | | 2.20 | 4.80 | 3.36 |
| -6'' | 4.24 | | | 5.80 | 6.10 | | 3.52 |
| -8 | 0.50 | 1.20 | | 0.64 | 0.50 | 1.14 | 0.72 |
| -8'' | | 0.50 | | | | 0.74 | |
| -2' | 0.36 | 1.42 | 0.56 | 0.08 | 0.40 | 0.04 | {-0.02} |
| -6' | 0 | 0.36 | | | | | |
| -2''' | -0.12 | -0.08 | | 0.52 | 0.20 | -0.14 | {0} |
| -6''' | | | | | -0.20 | | |
| -3' | | | 0.24 | 0.02 | -0.30 | 2.00 | {-0.10} |
| -5' | 0.10 | 0.52 | | | | | |
| -3''' | -0.08 | -0.06 | | 0.06 | 0.34*Me | -0.08 | {0.18} |
| -5''' | | | | | 0.03 | | |

* Tentative assignment.

symmetrical compound (14), because the co-ordination of $\text{Eu}(\text{fod})_3$ to the two flavone nuclei is not even but is characteristic of the structure of each compound. For example, a large difference is observed between MeO-5

The results in Table 2 may be summarized as follows: (a) the smallest S value for H-6 or -6'' is still larger than the largest S value for H-8 or -8''. Thus it is not difficult to distinguish signals due to H-6 or -6'' from those of

H-8 or -8''; (b) *S* values of H-3 or -3'' are so small that these protons are usually distinguishable from H-8 or -8'' in the same flavone nucleus; and (c) the smallest *S* values are observed for phenyl protons, although H-3' and -5' of compound (4) show a significantly larger *S* value (2.00 p.p.m.) than those of the other compounds because the phenyl group is attached to C-6 of the other flavone nucleus.

This method is potentially very useful for determination of the structures of new flavones. In the light of our results some of the reported assignments of hexa-*O*-methylagathisflavone (6)⁵ and hepta-*O*-methylsaharanflavone (7)⁷ should be revised as shown in Table 3. The corrected assignments of hexa-*O*-methylagathisflavone (6) were confirmed by n.O.e. studies as

TABLE 3

Correction of reported proton assignments

| Compound | δ | <i>S</i> Value | Corrected position | Reported position (τ) |
|----------|-------------------------|----------------|--------------------|------------------------------|
| (6) | 6.51 (s) | 5.80 | 6'' | 3 or 3'' (3.49) |
| | 6.53 (s) | 0.28 | 3'' | 3'' or 3 (3.47) |
| | 6.64 (s) | 0.06 | 3 | 6'' (3.36) |
| (7) | 6.80 (d, <i>J</i> 9 Hz) | 0.03 | 5''' | 3', 5' (3.20) |
| | 6.56 (d, <i>J</i> 3 Hz) | 0.50 | 8 | 6 (3.44) |
| | 6.38 (d, <i>J</i> 3 Hz) | 2.20 | 6 | 8 (3.62) |
| | 6.51 (s) | -0.44 | 3'' | 6'' (3.49) |
| | 6.39 (s) | 6.10 | 6'' | 3'' (3.61) |
| | 6.68 (d, <i>J</i> 9 Hz) | -0.30 | 3', 5' | 5''' (3.32) |

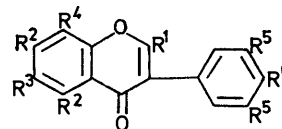
follows: on irradiation at the frequency of MeO-5'' (δ 4.06, the lowest methoxy-signal) enhancement was observed at the H-6'' signal, and on irradiation at the frequencies of MeO-7 (δ 3.80), MeO-7'' (3.88), and MeO-4''' (3.75), enhancements were observed at the H-8, H-6'', and H-3''' and -5''' signals, respectively. No effect was observed at the H-3 and -3'' signals on irradiation of any methoxy-signal.

The n.m.r. spectrum of the acetylation product of a new biflavone can be useful for determining the methoxy-position of a new member of a known biflavone group. However, the δ value of the methoxy-group of such an acetate is not the same as that of the corresponding methoxy-group of the fully methylated compound, and the acetates are not suitable for n.m.r. shift reagent studies. Therefore, trideuteriomethylation of a new biflavone followed by estimation of *S* values and comparison with those of known biflavone methyl ethers should be a good method for assigning the methoxy-position. As an example, trideuteriomethylation of sciadopitysin¹⁶ was carried out, giving the results shown in Table 4, which are in agreement with the structure, 4', 4''', 7-tri-*O*-methylamentoflavone. Although the structure of sciadopitysin can be deduced from δ values of the trideuteriomethylation product without *S* values, in some cases, such as hinokiflavone or ochnaflavone,¹⁷ *S* values are necessary for determining the methoxy-position because the methoxy-signals are very close to each other.

Isoflavones and Xanthenes.—Lanthanide-induced shift studies with Eu(fod)₃ were carried out with isoflavones

¹⁶ N. Kawano, *Chem. and Pharm. Bull. (Japan)*, 1959, **7**, 698, 821.

and xanthenes because these present some difficulties in structural elucidation similar to those in the case of flavones. The following five isoflavones were used to give the results shown in Table 5: 4', 5, 7-trimethoxy-



(15) R¹ = Me, R² = R⁶ = OMe, R³ = R⁴ = R⁵ = H

(16) R³ = Me, R² = OMe, R¹ = R⁴ = R⁵ = R⁶ = H

(17) R⁴ = Me, R² = OMe, R¹ = R³ = R⁵ = R⁶ = H

(18) R² = R³ = R⁵ = R⁶ = OMe, R¹ = R⁴ = H

(19) R² = OEt, R³ = R⁶ = OMe, R¹ = R⁴ = R⁵ = H

2-methylisoflavone (15), 5, 7-dimethoxy-6-methylisoflavone (16), 5, 7-dimethoxy-8-methylisoflavone (17), 3', 4', 5, 5', 6, 7-hexamethoxyisoflavone (18), and 5, 7-dimethoxy-4', 6-dimethoxyisoflavone (19). The results are mostly similar to those of flavones: (a) the largest shift

TABLE 4

N.m.r. data of tris-*O*-trideuteriomethylsciadopitysin

| Position | δ | <i>S</i> Value |
|-------------|------------|----------------|
| MeO-5 | 3.93 (s) * | |
| -5'' | 4.06 (s) * | |
| -7 | 3.87 (s) | 0.40 |
| -7'' | 3.93 (s) * | |
| -4' | 3.74 (s) | 0.12 |
| -4''' | 3.72 (s) | -0.08 |
| H-3 | { 6.57 (s) | { 0.04 |
| -3'' | { 6.63 (s) | { -0.18 |
| -6 | 6.32 (d) | 3.10 |
| -6'' | 6.50 (s) | 4.72 |
| -8 | 6.48 (d) | 0.56 |
| -2' | 7.85 (d) | 0.32 |
| -6' | 7.92 (q) | 0.04 |
| -2''', 6''' | 7.37 (d) | -0.14 |
| -5' | 7.12 (d) | -0.12 |
| -3''', 5''' | 6.75 (d) | -0.10 |

* δ Value of hexa-*O*-methylamentoflavone (12).

TABLE 5

 Δ_{Eu} Values (p.p.m.) of isoflavones with Eu(fod)₃

| Assigned position | Compounds | | | | |
|-------------------|-----------|---------|---------|---------|----------------|
| | (15) | (16) | (17) | (18) | (19) |
| 2 | [0.18] | -0.69 | -0.91 | -1.54 | -1.74 |
| 5 | (18.64) | (18.27) | (19.86) | (14.32) | (18.69) [8.65] |
| 6 | 6.99 | [5.04] | 8.43 | (7.79) | (4.61) |
| 7 | (0.77) | (0.75) | (1.95) | (1.65) | (0.95) [0.70] |
| 8 | 1.30 | 1.51 | [0.70] | 1.40 | 1.27 |
| 2', 6' | 0.10 | -1.68 | -0.54 | -1.31 | -2.53 |
| 3', 5' | 0.88 | -0.90 | 0.19 | (0.50) | -0.66 |
| 4' | (0.53) | -0.82 | 0 | (1.17) | (-0.14) |

CMe in square brackets, OMe or OCH₃ in parentheses; others are nuclear protons.

values are seen at MeO-5; (b) H-6, Me-6, or MeO-6 showed much greater downfield shifts than H-8 or Me-8, indicating a method for distinguishing positions 6 and 8; and (c) phenyl protons and H-2 showed smaller shifts. The CH₃-CH₂ shifts of compound (19) are similar to those of the methoxy-protons at position 5 or 7 of isoflavones or flavones.

¹⁷ M. Okigawa, N. Kawano, M. Aqil, and W. Rahman, *Tetrahedron Letters*, 1973, 2003.

Table 6 shows the Δ_{Eu} values of the following five xanthenes obtained by addition of $Eu(fod)_3$: 1,3,6-trimethoxyxanthone (20), 1,3,7-trimethoxyxanthone

TABLE 6

Δ_{Eu} Values (p.p.m.) of xanthenes with $Eu(fod)_3$

| Assigned position | Compounds | | | | |
|-------------------|-----------|---------|---------|---------|---------|
| | (20) | (21) | (22) | (23) | (24) |
| 1 | (15.97) | (20.16) | (19.44) | (8.46) | (10.06) |
| 2 | 7.31 | 8.87 | 8.30 | 3.46 | 3.87 |
| 3 | (1.32) | (1.40) | (1.30) | (0.49) | (0.52) |
| 4 | 1.83 | 2.03 | 1.75 | 0.38 | 0.56 |
| 5 | 0.16 | 0.01 | 0.04 | 0.80 | 0.56 |
| 6 | (-0.03) | -0.15 | (0) | 1.20 | (0.52) |
| 7 | -0.26 | (-0.36) | (-0.17) | 4.21 | 3.87 |
| 8 | -1.07 | -1.97 | -2.20 | (10.45) | (10.06) |

Me in parentheses; others are nuclear protons.

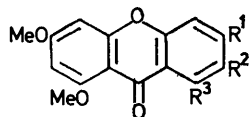
(20) $R^1 = OMe, R^2 = R^3 = H$

(21) $R^2 = OMe, R^1 = R^3 = H$

(22) $R^1 = R^2 = OMe, R^3 = H$

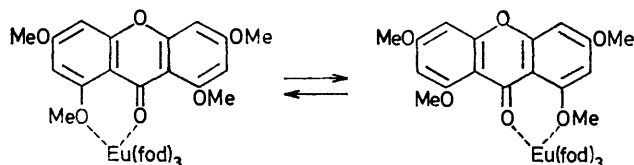
(23) $R^3 = OMe, R^1 = R^2 = H$

(24) $R^1 = R^3 = OMe, R^2 = H$



(21), 1,3,6,7-tetramethoxyxanthone (22), 1,3,8-trimethoxyxanthone (23), and 1,3,6,8-tetramethoxyxanthone (24). The relation between Δ_{Eu} values of H-2 and H-4 of these compounds is similar to that between those of H-6 and H-8 of 5,7-dimethoxy-flavones or -isoflavones. This implies that the method is similarly useful for the identification of xanthone derivatives. However, in the case of 1,8-dimethoxy-compounds [(23) and (24)] the Δ_{Eu} values of H-2 are much smaller than those of 1-methoxy-compounds, indicating that the Eu^{III} co-ordinates to both the carbonyl oxygen atom and one of the neighbouring methoxy-oxygens (see Scheme, in which the co-ordination number¹⁸ of Eu^{III} is 8).

Difference in Co-ordination States of $Eu(fod)_3$ and $Eu(dpm)_3$.—The Δ_{Eu} values of H-3 and H-6 (Table 1) of tri-*O*-methylapigenin (8) are markedly different from one another when $Eu(fod)_3$ is used, but almost the same in the case of $Eu(dpm)_3$. A similar difference between



SCHEME

$Eu(fod)_3$ and $Eu(dpm)_3$ is seen with compounds (9)—(11), indicating the considerable difference in the co-ordination geometry of the two shift reagents. The difference in Δ_{Eu} values between the two reagents seems to be caused by the predominant co-ordination of $Eu(fod)_3$ to the ether oxygen atom of a 5-methoxy-group rather than a carbonyl oxygen atom. Recently, King and his co-

¹⁸ A. M. Grotens and J. Smid, *Tetrahedron Letters*, 1971, 8463.

¹⁹ H. Cairns, D. Hunter, J. King, and N. H. Rogers, *Tetrahedron*, 1974, 30, 79.

workers¹⁹ reported a similar observation: that the oxygen atom of a 5-alkoxy-substituent is the predominant co-ordination site in ethyl 4-oxo-4*H*-1-benzopyran-2-carboxylates.

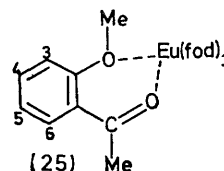
However, no co-ordination was observed at any ether oxygen atom other than the 5-methoxy-group of these flavones, and it is reported²⁰ that ketones have a greater ability to co-ordinate and cause a lanthanide-induced shift than ethers. In order to examine the matter with simpler compounds, 2- and 4-methoxyacetophenone were studied; the results are shown in Table 7. In the *para*-substituted compound the acetyl

TABLE 7

Δ_{Eu} Values (p.p.m.) of methoxyacetophenones with $Eu(fod)_3$ and $Eu(dpm)_3$

| Protons | 2-OMe | | 4-OMe | | |
|---------|-------------|-------------|-------------|-------------|------|
| | $Eu(fod)_3$ | $Eu(dpm)_3$ | $Eu(fod)_3$ | $Eu(dpm)_3$ | |
| Ac | 5.78 | 6.31 | Ac | 7.92 | 7.00 |
| MeO | 7.55 | 2.12 | MeO | 0.80 | 0.81 |
| H-3 | 4.50 | 2.00 | H-3,5 | 1.68 | 1.58 |
| H-4 | 1.69 | 1.28 | H-2,6 | 6.59 | 5.90 |
| H-5 | 1.72 | 1.44 | | | |
| H-6 | 6.41 | 8.47 | | | |

protons showed the largest shift and very little difference was seen between the two shift reagents. On the contrary, in the *ortho*-substituted compound a large difference between $Eu(fod)_3$ and $Eu(dpm)_3$ was observed. When $Eu(fod)_3$ was added the largest Δ_{Eu} value was seen with the methoxy-signal, with progressively smaller shifts of the H-6 and acetyl signals. This suggests the co-ordination structure (25) in which the Eu^{III} is located so as to have more effect on the methoxy-than the acetyl protons. On the other hand, the fact that the Δ_{Eu} value of H-6 of the same compound (25) is

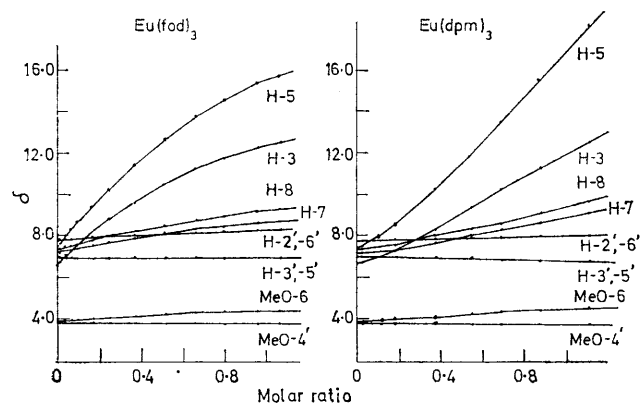


larger than that of H-3 suggests the strong co-ordinating ability of the carbonyl oxygen atom. In the case of $Eu(dpm)_3$, the acetyl protons showed about a three times greater value than the methoxy-protons, indicating predominant co-ordination of Eu^{III} to carbonyl oxygen with co-ordination number 7.

As already described for the case of biflavones, S values were the same as Δ_{Eu} values when $Eu(fod)_3$ was added, because the plotted lines are almost straight. However, in the case of 4',6-dimethoxyflavone, which bears no 5 methoxy-group, curvature was seen, especially when more than 0.5 mol. equiv. of $Eu(fod)_3$ was added (Figure). This can be explained by the formation of a 2:1 co-ordination compound (co-ordination number 8) at low concentration of $Eu(fod)_3$ and then of a 1:1

²⁰ J. K. M. Sanders and D. H. Williams, *J. Amer. Chem. Soc.*, 1971, 93, 641.

compound (co-ordination number 7) after addition of more than 0.5 mol. equiv. of $\text{Eu}(\text{fod})_3$. This is supported



by the fact that little difference was observed between the two shift reagents in the case of 4',6-dimethoxyflavone (Table 8). Accordingly, a main reason for the

difference in co-ordination state between $\text{Eu}(\text{fod})_3$ and $\text{Eu}(\text{dpm})_3$ seems to be that the former is apt to form an intramolecular co-ordination compound with co-ordination number 8 in the case of 5-methoxychromone and related derivatives, whereas the latter generally co-ordinates to form a compound with co-ordination number 7.

EXPERIMENTAL

N.m.r. spectra were recorded with a JEOL PS-100 instrument for solutions of 7—15 mg (mostly 10—12 mg) of substance in 500 μl of CDCl_3 .

Trideuteriomethylation of Sciadopitysin.—Ethereal diazomethane (15 ml) [prepared from nitrosomethylurea (10 g)] was mixed with dioxan (20 ml) and D_2O (2 ml) and cooled for 4 h in ice. Sciadopitysin (30 mg) in dioxan (30 ml) and D_2O (0.1 ml) was added, and after 2 days the solvent was distilled off and the residue purified by column chromatography on silica gel (Mallinckrodt; 100 mesh; 5 g) with chloroform as eluant. Recrystallization from methanol gave pale yellow crystals (18 mg), m.p. 198—213°.

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TABLE 8
 Δ_{Eu} Values of 4',6-dimethoxyflavone

| Protons | δ | Δ_{Eu} (p.p.m.) | |
|---------|----------|-------------------------------|---------------------------|
| | | $\text{Eu}(\text{fod})_3$ | $\text{Eu}(\text{dpm})_3$ |
| MeO-6 | 3.88 (s) | 0.42 | 0.72 |
| -4' | 3.85 (s) | -0.03 | -0.05 |
| H-3 | 6.70 (s) | 5.68 | 5.34 |
| -7 | 7.23 (q) | 1.45 | 1.59 |
| -8 | 7.45 (d) | 1.71 | 1.95 |
| -5 | 7.55 (d) | 8.00 | 9.47 |
| -3',5' | 6.99 (d) | 0 | -0.14 |
| -2',6' | 7.83 (d) | 0.47 | 0.19 |