Chemotaxonomy of the Rutaceae. IV.[1] Constituents of *Murraya paniculata* (Linn.) Jack.

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8-Isopentenyllimettin (2) and 3,3',4',5,5',6,7-heptamethoxyflavone (11) have been isolated from *Murraya paniculata* (Linn.) Jack. The synthesis of both 8-isopentyl- and 8-isopentenyllimettin is described.

Murraya is a genus of the family Rutaceae, native to Southeast Asia.[4] Species of this genus have been the subject of several previous chemical investigations.[5,6] Extracts from the dried foliage of *Murraya paniculata* (Linn.) Jack. (*M. exotica L.*) were employed in the present study. Chromatography on alumina gave a new coumarin and a permethylated flavone. Analysis of the coumarin, mp 157–158°, showed $C_{16}H_{18}O_4$. Its uv spectrum was very similar to that of 5,7-dimethoxycoumarin (limettin).[7] The nmr spectrum showed the usual coumarin AB doublet for H-3 and H-4, a one-proton aromatic singlet as well as resonances for two methoxy groups and an isopentenyl side chain. The chemical shift of the methylene resonance indicated the isopentenyl group was attached directly to the aromatic ring and not through an ether oxygen. These data can be accommodated by structures **1** or **2**.

Toddaculine (**1**), mp 95°, has previously been reported as a constituent of *Toddalia aculeata* Pers., another rutaceous plant.[8] Since the observed melting point is different from that reported for toddaculine (**1**), structure **1** can be rejected for the coumarin isolated in this study, leaving only **2** for consideration. Toddaculine (**1**) has been hydrogenated to a tetrahydro derivative (**3**), mp 75°. The potential reduction product of **2**, a C-8 isomeric tetrahydro derivative (**4**), has been obtained from another coumarin (**5**).[9] Compound **4** showed mp 87–88.5°. Hydrogenation of the natural coumarin (**2**) was difficult to control, especially at the dihydro stage, but it was possible to isolate small amounts of **6**. This dihydro derivative was identical with 8-isopentyllimettin (**6**) previously prepared from its naturally occurring 2'-oxo derivative (**5**).[9] See Scheme I.

The structure of the dihydro derivative (**6**) was further confirmed by synthesis from the known 2-isopentyl-3,5-dimethoxyphenol (**7**).[10] Several unsuccessful synthetic attempts leading to **6** have been previously described.[9] A Duff reaction[11] with 2-isopentyl-3,5-dimethoxyphenol (**7**) did not prove rewarding. There appears to be little information on the utility of the Vilsmeier formylation reaction for the preparation of aldehydes from phenols. The Vilsmeier reaction gave the desired salicaldehyde (**8**) in 85–90% yield. The aldehyde gave a strong ferric test, and its ultraviolet spectrum was very similar to that of 4,6-dimethoxysalicaldehyde (**9**), showing that formylation had occurred *ortho* to the phenol. The *ortho* substitution may account for the exceptional ease of hydrolysis of the carbinolamine intermediate of the Vilsmeier reaction (see Experimental Section). A Knoevenagel condensation of **8** with malonic acid gave the desired coumarin (**6**) in poor yield, identical with that obtained from **2** by hydrogenation or previously obtained from **5**.[9] See Scheme II.

Direct evidence for the structure of the natural coumarin (**2**) occurring in *Murraya* was obtained by synthesis using a route modeled after Späth and Holzen's synthesis of osthol.[12] Thus, 4,6-dimethoxysalicaldehyde (**9**) was alkylated with isopentenyl bromide under conditions favoring C alkylation[13] to give **10**. Even though the yield from alkylation in water was only about 15%, this method represented a significant improvement over alkylation in benzene by a procedure originally described by Späth and Holzen.[12] A Perkin reaction[14] of **10** gave the desired coumarin (**2**) in poor yield.

An nmr spectrum of the permethylated flavone isolated from the extracts indicated that it was a heptamethoxy derivative. The unfavorable overlapping of the methoxy resonances was partially overcome by taking the spectrum in benzene in which the methoxy resonances were nicely separated.[15] The aromatic region of the nmr spectrum showed only a one-proton and a two-proton singlet. The chemical shift of the two-proton singlet (δ 7.37) was very similar to that for the 2' and 6' protons of myricetin hexamethyl ether (δ 7.33). This arrangement suggested a symmetrically substituted 3',4',5'-trimethoxy B ring. The one-proton singlet could be assigned to either a 3 or 8 proton. Demethylation of the flavone with 20% hydrochloric acid gave the 5-demethyl derivative (**12**) in which the one-proton singlet moved upfield. Acet-

(1) Part III: D. L. Dreyer, *J. Org. Chem.*, **33**, 3658 (1968).

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(4) For a review of the botany of the genus *Murraya*, see W. T. Swingle, "The Citrus Industry," Vol. 1, H. H. Webber and D. L. Batcheler, Ed., University of California Press, Berkeley, Calif., 1943, p 192.

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(7) H. Bohme and T. Severin, *Arch. Pharm.*, **290**, 486 (1957).

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(9) D. L. Dreyer, *Tetrahedron*, **23**, 4613 (1967).

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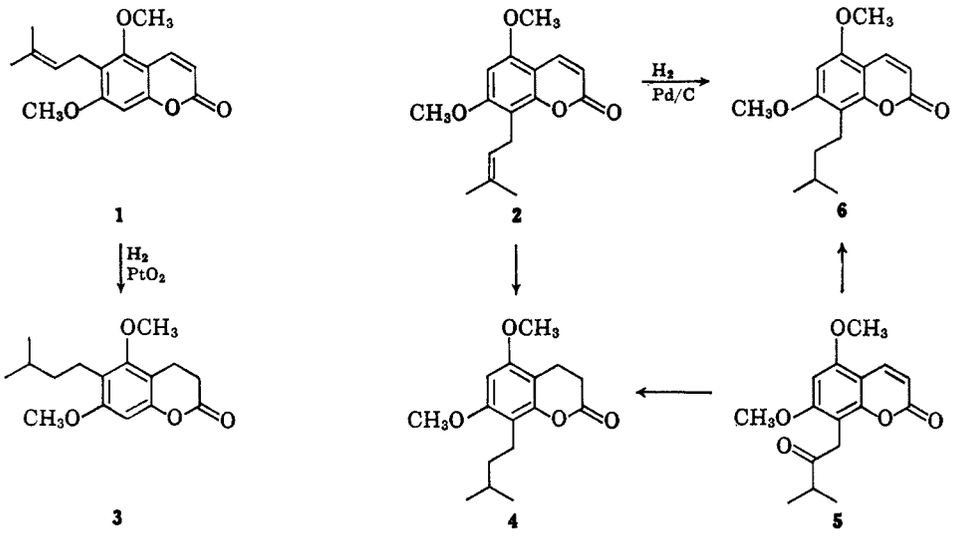
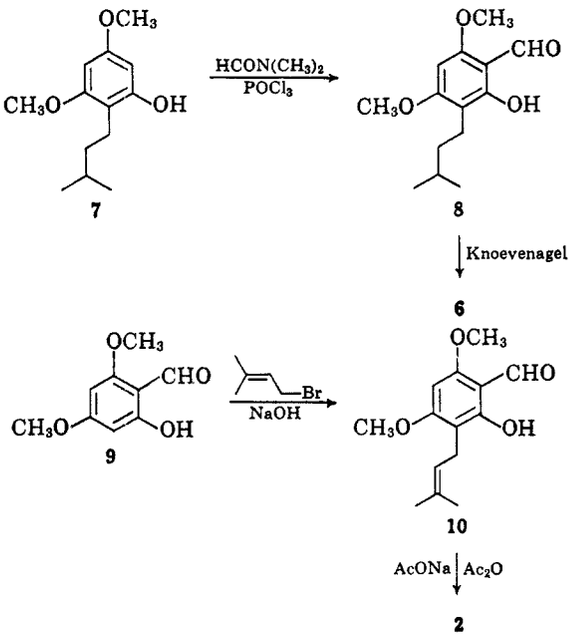
(14) See, for example, E. Späth, Z. Jerzmanowska-Sienkiewiczowa, *Chem. Ber.*, **70**, 698 (1937).

(15) H. M. Fales and K. S. Warren, *J. Org. Chem.*, **32**, 501 (1967).

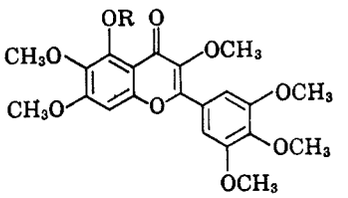
SCHEME I



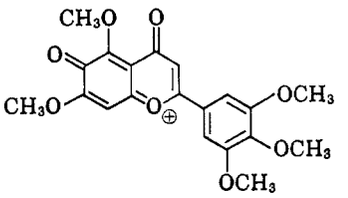
SCHEME II



structure. The strong molecular ion at *m/e* 432 (60) is accompanied by the base peak at *m/e* 417. As in the case of other 6-methoxy flavones this intense M − 15 peak is ascribed to a structure of the type **14**.[16,19]



11, R = CH_3
12, R = H
13, R = AcO



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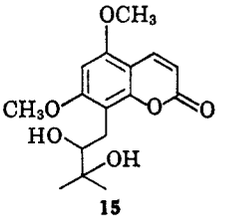
ylation of the 5-hydroxy derivative (**12**) gave a monoacetate (**13**) which showed a downfield shift of the one-proton singlet. This pattern of shifts is only consistent with an 8 proton. As the resonance of a 3 proton in flavones is independent of such chemical changes,[16] a 3-methoxy group must be present. Detailed considerations of the benzene solvent shifts of the heptamethoxyflavone indicate that the methoxy groups are located in the 5, 6, and 7 positions.[17]

At this stage of the work it became apparent that the probable structure, 3,3′,4′,5′,5,6,7-heptamethoxyflavone (**11**), had previously been prepared by Jefferies, *et al.*[18] Comparison of the flavone isolated from *Murraya* with an authentic sample provided by Professor Jefferies showed complete identity. The mass spectrum of the flavone is consistent with the proposed

The heptamethoxyflavone (**11**) was also present in the fruit of *Murraya paniculata*.[20]

The isolation of the coumarin (**2**), called coumarrayin, from *M. paniculata* also has recently been reported.[21] The results obtained in this study differ in detail from those observed by Chakraborty, *et al.*,[6] who reported the isolation of mexoticin (**15**), a 2′,3′-diol of **2** from



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(16) *Cf.* zapotin, zapotinin, and zapotinin acetate: D. L. Dreyer, *J. Org. Chem.*, **33**, 3577 (1968).

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

(18) P. R. Jefferies, J. R. Knox, and E. J. Middleton, *Aust. J. Chem.*, **15**, 532 (1962).

(19) D. L. Dreyer and D. J. Bertelli, *Tetrahedron*, **23**, 4607 (1967).

(20) Henry Yokoyama, private communication, 1967.

(21) E. Ramstad, W. C. Lin, T. Lin, and W. Koo, *Tetrahedron Lett.*, 811 (1968). In this case the position of the isopentenyl group was made by application of the Gibb's test, a procedure of uncertain reliability: E. D. Burling, A. Jefferson, and F. Scheinmann, *Tetrahedron*, **21**, 2653 (1965).

M. exotica L. (*M. paniculata*). Such a result is not surprising in view of the close structural relationship between **2** and **15** although no evidence for the presence of **15** was found in the present study. The coumarin (**2**) is an obvious biogenetic intermediate in the formation of mexoticin (**15**). It is not clear if the compositional differences found in the two different studies are due to some climatic, seasonal, geographical, or genetic difference in the plant material used.

Experimental Section[22]

Isolation.—Dried and ground foliage of *Murraya paniculata* (Linn.) Jack., collected at the Citrus Research Center, University of California at Riverside, was extracted with acetone. The solvent was removed from the extracts, and the residue was chromatographed on alumina. The fractions from the column were monitored by silicic acid tlc. The spots were detected by inspection under ultraviolet light. Permethylated flavones could be distinguished as yellow spots by fuming with HCl gas. Hexane eluted large amounts of oils. A mixture of 10% benzene in hexane eluted a coumarin. Combination of fractions containing the blue fluorescent spot and crystallization of the residue from ethyl acetate–hexane gave the coumarin (**2**). A sample was sublimed for analysis and recrystallized from ethyl acetate–hexane: mp 157–158°; λ_{max}^{EtOH} mμ 206, 260, 324; nmr, δ 7.92 (d, J = 9, H-4), 6.32(s) H-6, 6.01(d) (J = 9), H-3, 5.20(t) (J = 7), vinyl, 3.93(s) methoxy, 3.43(d) (J = 7), α-methylene, 1.83, 1.60 C-methyls ($CDCl_3$).

Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61. Found: C, 70.1; H, 6.61.

Fractions eluted from the column with benzene gave a bright yellow spot on tlc when fumed with HCl gas. These fractions were combined, solvent was removed, and the residue was crystallized from EtOAc–hexane and then methanol to give the heptamethoxyflavone (**11**): mp 156–157° (lit.[18] mp 155–156°); λ_{max}^{EtOH} 213 mμ (ε 72,000), ~235 (21,000), ~260 (15,000), 324 (24,000); prominent mass spectrometry peaks occurred at m/e 95(5), 96(5) 97(10), 98(6), 111(6), 129(6), 359(6), 371(4), 387(4), 399(5), 401(17), 417(100), 418(24), 419(5), 431(17), 432(60), 433(15); nmr, δ 7.37(s) H-2′ and H-6′, 6.77(s) H-8, 4.02, 4.02, 3.96, 3.96, 3.96, 3.92 3.88 methoxys ($CDCl_3$); δ 4.03, 3.87, 3.87, 3.80, 3.65, 3.65, 3.42 methoxys (benzene).

Anal. Calcd for $C_{22}H_{24}O_9$: C, 61.10; H, 5.59. Found: C, 61.1; H, 5.58.

5-Hydroxy-3,3′,4′,5′,6,7-hexamethoxyflavone (**12**).—A suspension of 0.55 g of flavone was boiled with 20% HCl. The material went into solution in about 15 min and the product began to crystallize on further heating. After 25 min the solution was cooled and the product was collected by filtration: mp 174–176°, from methanol (lit.[18] mp 176–178°): green ferric chloride; λ_{max}^{EtOH} 210, 271, 332 mμ; $\lambda^{EtOH-NaOH}$ 296, 380 mμ; nmr, δ 7.38(s) H-2′ and H-6′, 6.52(s) H-8, 3.97, 3.97, 3.97, 3.97, 3.93, 3.88 methoxys ($CDCl_3$).

5-Acetoxy-3,3′,4′,5′,6,7-hexamethoxyflavone (**13**).—The acetate was prepared with acetic anhydride–pyridine: mp 183–184°, from benzene (lit.[18] mp 177–178°); λ_{max}^{EtOH} 214, ~235, ~255, 323 mμ; nmr, δ 7.35(s) H-2′ and H-6′, 6.87(s) H-8, 4.00, 3.95, 3.95, 3.95, 3.87, 3.82 methoxys, 2.52 acetoxy ($CDCl_3$); δ 3.87, 3.78, 3.77, 3.57, 3.57, 3.18 methoxys, 2.40 acetoxy (benzene).

Myricetin Hexamethyl Ether.—Nmr showed δ 7.39(s), H-2′ and H-6′, 6.52, 6.37 (AB doublet) (J = 2), H-6 and H-8, 3.97, 3.95, 3.95, 3.95, 3.95, 3.92 methoxys ($CDCl_3$); δ 3.88, 3.88, 3.57, 3.57, 3.44, 3.32 methoxys (benzene).

3-Isopentyl-4,6-dimethoxysalicaldehyde (**8**).—The Vilsmeier reagent was prepared by slowly adding 5 ml of $POCl_3$ to 40 ml of dimethylformamide with cooling. To this cold solution was added 1 g of 2-isopentyl-3,5-dimethoxyphenol,[10] and the mixture was shaken to effect solution. The solution was warmed on a steam bath for 20 min, allowed to cool, and decomposed with ice. A large volume of water was added and the mixture was extracted with benzene. The benzene phase was dried, the solvent was removed, and the residue was filtered through a short column of alumina with chloroform. The solvent was removed from the filtrates and the residue was crystallized twice from methanol: mp 85–87° (85–90% yield); brown black ferric chloride; λ_{max}^{EtOH} 297 mμ.

Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99. Found: C, 66.8; H, 7.96.

8-Isopentyllimettin (**6**).—To a solution of 120 mg of **8** in 1 ml of piperidine and 10 ml pyridine was added 0.5 g of malonic acid and the solution was heated on a steam bath for 6 hr. A further 0.5 g of malonic acid was then added and heating continued a further 4 hr. Dilute HCl was added to the cooled solution, and it was extracted thoroughly with benzene. The concentrated benzene extracts were filtered through a short column of alumina and eluted with further amounts of benzene until the fractions showed no further fluorescence. Solvent was removed from those fractions showing blue fluorescence under ultraviolet light and the residue was crystallized from ethyl acetate–hexane, mp 144–144.5°;[23] ultraviolet and infrared spectra were identical with those obtained from the hydrogenation product of **2**.

3-Isopentenyl-4,6-dimethoxysalicaldehyde (**10**).—To a solution of 10 g of 4,6-dimethoxysalicaldehyde (**9**) in 60 ml of benzene was added 2 g of 50% sodium hydride in oil. After refluxing for 30 min on a steam bath, a solution of 6 g of γ,γ-dimethylallyl bromide[24] in 20 ml of benzene was added and the mixture was refluxed a further 6 hr. The mixture was decomposed with water and the benzene layer was washed with further 5% aqueous NaOH and water and dried. Solvent was removed and the residue was chromatographed on alumina. Hexane eluted the oil, and the product (**10**) was obtained by elution with 10% benzene in hexane: mp 105–107°, from hexane; black ferric chloride; λ_{max}^{EtOH} 214 mμ (ε 20,800), ~230 (12,300), 297 (20,800), ~332 (4000); nmr, δ 10.05(s) aldehyde, 5.85(s) aromatic, 5.10(t) (J = 7), vinyl, 3.87, 3.84 methoxys, 3.17(d) (J = 7), methylene, 1.70, 1.65 C-methyls ($CDCl_3$).

Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.6; H, 7.29.

Fractions following from the column yielded the O-isopentenyl derivative of **10**: mp 78–80°, from hexane; nmr, δ 10.01(s) aldehyde, 7.22(s) aromatic, 5.52(t) (J = 7), O—CH_2**CH**=, 5.05 (t) (J = 7), ArCH_2**CH**=, 4.19(d) (J = 7), O—**CH_2**CH=, 3.87, 3.84 methoxys, 3.20(d) (J = 7), Ar**CH_2**CH=, 1.78, 1.72, 1.68, 1.68 C-methyls ($CDCl_3$).

Anal. Calcd for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.8; H, 8.23.

Substantial amounts of starting material (**9**) were recovered by acidification of the base washings.

Compound **10** was more conveniently prepared by dissolving 10 g of **9** in 30 ml of water containing 2.2 g of NaOH. To this stirred solution was added 7.65 g of isopentenyl bromide, and stirring was continued for 3 hr at room temperature. After standing overnight the reaction was extracted with chloroform. The chloroform extracts were washed with 5% NaOH and dried, and the solvent was removed to give 1.5 g of **10**, identical with that prepared by alkylation in benzene.

8-Isopentenyllimettin (**2**).—A solution of 60 mg of **10** in acetic anhydride was refluxed with 200 mg of anhydrous NaOAc at 160° for 24 hr. The cooled solution was poured into water and extracted with chloroform. Solvent was removed from the dried chloroform extracts and the residue was filtered through a short column of alumina with benzene. Removal of solvent from the filtrates gave 10 mg of product after recrystallization from ethyl acetate–hexane: mp 158–158.5°; mmp 156–158°. Ultraviolet and infrared spectra were superimposable on those of the natural material.

Registry No.—**2**, 17245-25-9; **6**, 17245-26-0; **8**, 17245-27-1; **10**, 17245-28-2; O-isopentenyl derivative of **10**, 17245-29-3; **11**, 17245-30-6; **12**, 17245-31-7; **13**, 17245-32-8.

Acknowledgment.—The author is indebted to Professor P. R. Jefferies for an authentic sample of heptamethoxyflavone, to L. M. White for the analytical data, and to Dr. R. M. Horowitz for helpful discussions.

(22) Nmr spectra were taken at 60 MHz. The relative areas of the peaks were consistent with the assignments. J values are in hertz.

(23) The melting point given in ref 9 for **6** is in error and should be 138.5–140°.

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