SYNTHESIS OF NATURALLY OCCURRING PARTIAL METHYL ETHERS OF MYRICETIN

P. N. SARMA, G. SRIMANNARAYANA AND N. V. SUBBA RAO

(*Department of Chemistry, Osmania University, Hyderabad* 500007)

MS received 10 May 1974; after revision 28 June 1974

ABSTRACT

The synthesis of combretol, annulatin, and europetin naturally occurring partial methyl ethers of myricetin is described. Condensation of 2, 4, 6-trihydroxy-ω-methoxyacetophenone with tri O methyl galloyl chloride or tri-O benzyl galloyl chloride furnished the appropriate 3-methoxyflavones, which by a series of reactions furnished the natural myricetin derivatives.

MYRICETIN occurs in many plants either in free state or as glycosides. Murti, Rao and Seshadri[1] reported that hexamethyl ether of myricetin exhibited fish-toxic properties. No partial methyl ether of myricetin was reported to occur in nature till 1960. During the last decade six partial methyl ethers of myricetin were found to occur either in free state or as glycosides in plant materials. The naturally occurring partial methyl ethers of myricetin and their sources are given in Table I.

TABLE I

Naturally occurring partial methyl ethers of myricetin

Name	Position of Methylation	Source
Annulatin ..	3	Aegialitis leaf[2]
5-O-Methyl myricetin ..	5	Rhododendron petals[3]
Europetin ..	7	Plumbago leaf[2]
Syringetin ..	3′, 5′	Lathyrus petals[4] *Soymida febrigua* root[16]
3, 7, 4′-Tri-O-methylmyricetin	3, 7, 4′	Ricinocarpus leaf[5]
Combretol ..	3, 7, 3′, 4′, 5′	Combretum seeds[6]
Mearnisitrin ..	4′	*Acacia mearnsi* leaf[7]

Some of these compounds were available only in small quantities. Therefore, often their structures were established by physical methods. Their fish-toxic properties do not seem to have been investigated. In this connection, it is interesting to note that the naturally occurring polyhydroxy flavonol, calycopterin exhibits anthelmintic properties.[8] These considerations prompted us to undertake the synthesis of some naturally occurring partial methyl ethers of myricetin such as combretol (IV), annulatin (V) and europetin (VIII) with a view to test their fish-toxic properties. Incidentally, the present investigation gave an opportunity to confirm the structures assigned earlier to these compounds.

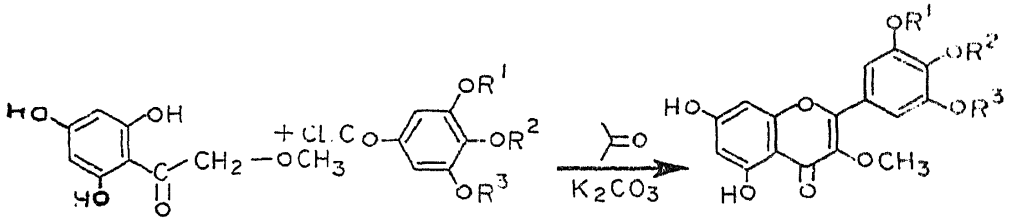
Allan-Robinson method[9] was the method of choice for the synthesis of naturally occurring flavonols. Modified Baker-Venkataraman transformation has not been exploited for the synthesis of 3-methoxyflavones[10–13]. This method consists of refluxing *o*-hydroxy-ω-alkyl, aryl or methoxy acetophenones with an appropriate aromatic acid chloride in acetone-potassium carbonate medium. This method has now been employed in the synthesis of partial methyl ethers of myricetin.

Combretol, 3, 3′, 4′, 5′, 7-pentamethoxy-5-hydroxyflavone (IV) is an extractive of *Combretum quadrangulare*. ω-Methoxy phloroacetophenone (I) was refluxed with tri-O-methyl galloyl chloride (II-1) in acetone-potassium carbonate medium for 10 hr. The crude product obtained was subjected to mild hydrolysis to yield 5, 7-dihydroxy-3, 3′, 4′, 5′-tetramethoxy flavone (III-1) in 75% yield. This was subsequently mono-methylated with dimethyl sulphate in acetone-potassium carbonate medium to yield combretol (IV), identical in all respects with an authentic sample of combretol procured through the courtesy of Dr. K. Y. Sim. The synthesis of combretol by Allan-Robinson method[14] was subsequently reported.

Annulatin, 3′, 4′, 5′, 5, 7-pentahydroxy-3-methoxyflavone, was isolated from the leaf of *Aegialitis annulata* as a glycoside.[2] Its synthesis has been once again achieved by adopting Baker-Venkataraman transformation. Refluxing ω-methoxyphloroacetophenone (I) with tri-O-benzyl galloyl chloride (II-2) yielded the corresponding flavone (III-2). This was later debenzylated with a mixture of acetic acid/HCl to yield annulatin (V). Annulatin was synthesised by the Allan-Robinson method[15] much before its isolation from plant source.

Europetin, 7-O-methylmyricetin (VIII) is a naturally occurring flavonol found as glycoside in *Plumbago europea*.[2] Its synthesis has now been achieved. 5, 7-Dihydroxy-3′, 4′, 5′-tri-O-benzyl-3-methoxyflavone (III-2) has been

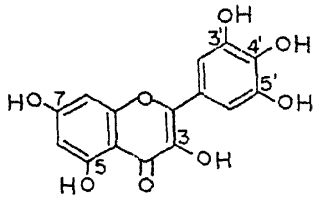
monomethylated and subsequently debenzylated to produce 3, 7 dimeth ether of myricetin (VII). Compound (VII) has not so far been isolated fro plants. Selective demethylation of (VII) has been effected by heating wi pyridine–hydrochloride to produce europetin (VIII).



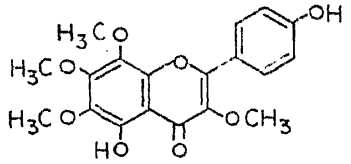
I

II-(1) $R^1=R^2=R^3=-CH_3$ III-(1) $R^1=R^2=R^3=-CH_3$

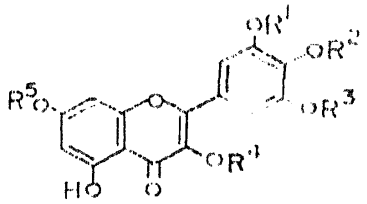
II-(2) $R^1=R^2=R^3=-CH_2-Ph$ III-(2) $R^1=R^2=R^3=-CH_2-Ph$



MYRICETIN



CALYCOPTERIN



IV $R^1=R^2=R^3=R^4=R^5=CH_3$

V $R^1=R^2=R^3=R^5=-H$; $R^4=CH_3$

VI $R^1=R^2=R^3=-CH_2-Ph$, R^4 $R^5=-CH$

VII $R^1=R^2=R^3=-H$, R^4 $R^5=CH_3$

VIII $R^1=R^2=R^3=R^4=-H$, $R^5=CH_3$

Natural annulatin and europetin could not be procured but their physic and U.V. data, presented in experimental, are found to be identical wi those of synthetic samples. A partial synthesis of europetin was made l Harborne[2] starting from natural myricetin–3–rhamnoside. Therefore, t present synthesis of europetin constitutes an unambiguous synthesis.

In all these syntheses, the yields of the flavonols are good (60–70% indicating the facile nature of modified Baker-Venkataraman transformatic and the products are easy to work up. The intermediate diketones cou not be isolated and only direct formation of flavones was observed. Ther fore, for the synthesis of 3–methoxyflavones modified Baker–Venkatarama transformation may be considered as a very convenient method.

Experimental Procedure

Myricetin 3, 3′, 4′, 5′*–tetramethyl ether (III–1)*

Anhydrous 2, 4, 6–trihydroxy–ω–methoxyacetophenone (I) (2·0 g) w refluxed in dry acetone solution (250 ml) with tri–O–methyl galloyl chlori

(7·6 g) and anyhydrous potassium carbonate (25·0 g) for 10 hr. during which time the solution turned yellow. The solvent was removed and to the cooled residue aqueous potassium carbonate (5%, 100 ml) was added. Ethanol was added (250 ml) to the suspension until a homogeneous solution was obtained and the whole solution refluxed for one hour. Ethanol was removed under reduced pressure, the residue treated with cold water and filtered. The clear filtrate was saturated with carbon dioxide when a yellow solid separated. It was crystallised from alcohol as light yellow needles (3·0 g), m.p. 279° C (Found C, 60·8%, H, 4·8%; $C_{19}H_{18}O_8$ requires C, 60·9%; H, 4·8%).

Combretol (*Myricetin* 3, 3′, 4′, 5′, 7–*pentamethyl ether* (*IV*)

A mixture of myricetin–3, 3′, 4′, 5′–tetramethyl ether (1·0 g) dry acetone (200 ml), dimethyl sulphate (0·2 ml) and anhydrous potassium carbonate (5·0 g) was refluxed for 7 hr on a water-bath. At the end of the reaction acetone was removed, sufficient water was added and neutralised with dilute hydrochloric acid. The precipitate was filtered and crystallised from alcohol as light yellow needles (0·92 g), m.p. 144° C. The sample is identical in all respects with an authentic sample supplied by Dr K. Y. Sim (m.p., mm.p. and ir), U.V. λ_{max}^{EtOH} 266 (log ϵ 4·14), 343 nm (log ϵ 4·15).

3–*Methoxy* 3′, 4′, 5′–*tribenzyloxy*–5, 7–*dihydroxyflavone* (*III–2*)

Anhydrous 2, 4, 6–trihydroxy–ω–methoxyacetophenone (2·0 g) and tri–O benzyl galloyl chloride (14·0 g) were dissolved in dry acetone (200 ml) and treated with anhydrous potassium carbonate (20·0 g). The mixture was refluxed for 15 hr. The reaction product was worked out as in the case of compound (III–1). The pale yellow solid obtained was crystallised from alcohol as light yellow needles (3·5 g), m.p. 240° C (Found: C, 73·8%; H, 5·2%; $C_{37}H_{30}O_8$ requires C, 73·7%; H, 4·9%).

3, 7–*Dimethoxy*–3′, 4′, 5′–*tribenzyloxy*–5–*hydroxyflavone* (*VI*)

3–Methoxy–3′, 4′, 5′–tribenzyloxy–5, 7–dihydroxyflavone (0·7 g) was methylated with dimethyl sulphate (0·5 ml) in acetone (150 ml) containing dry potassium carbonate (5·0 g) for 7 hr. The reaction product was worked up as in the case of compound (IV). The solid obtained was crystallised from alcohol as yellow needles (0·5 g), m.p. 132° C. (Found C, 74·1%; H, 5·1%; $C_{38}H_{32}O_8$ requires C, 74·0%; H, 5·1%).

Myricetin 3, 7-*dimethyl ether* (*VII*)

3, 7–Dimethoxy–3′, 4′, 5′–tribenzyloxy–5–hydroxyflavone (0·4 g) was dissolved in acetic acid (5 ml) and concentrated hydrochloric acid (5 ml) added. The solution was heated on a water-bath for five minutes and poured into crushed ice. The resulting product was crystallised from alcohol as pale yellow needles (0·3 g), m.p. 235° C (Found C 59·2%; H, 4·1%; $C_{17}H_{14}O_8$ requires C, 59·4%; H, 4·2%), U.V. λ_{max}^{EtOH} 260 (log ε 4·15) 353 nm (log ε 4·23).

Annulatin (*Myricetin–3–methyl ether*) (*V*)

3–Methoxy–3′, 4′, 5′–tribenzyloxy–5, 7–dihydroxyflavone was dissolved in glacial acetic acid (5 ml) and concentrated hydrochloric acid (5 ml) was added. The solution was heated for forty-five minutes on a water-bath and the product was worked up as described above. The crude product was crystallised from alcohol as light yellow needles (0·1 g), m.p. 320° C, U.V. λ_{max}^{EtOH} 257 (log ε 4·03), 362 nm (log ε 4·04).

Europetin (*Myricetin–7–methyl ether*) (*VIII*)

3, 7–Dimethyl ether of myricetin (0·2 g) was mixed with pyridine hydrochloride (5·0 g) and the mixture was heated in a oil-bath at 130° C, for 2 hr. At the end of the reaction, the mixture was poured on crushed ice. The resulting solid was filtered, washed thoroughly with water. The dried product was crystallised from alcohol as greenish-yellow needles (0·09 g) m.p. 278° C, (Found: C, 57·8%; H, 3·7%; $C_{10}H_{12}O_8$ requires C, 57·7%; H, 3·6%), U.V. λ_{max}^{EtOH} 256 (log ε 4·09), 375 nm (log ε 4·16).

ACKNOWLEDGEMENT

One of the authors (P. N. S.) is thankful to the U.G.C. for the award of a fellowship.

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