dl-MARINDININ (DIHYDROKAWAIN) AND SOME RELATED 6-ARYL-5, 6-DIHYDRO-4-METHOXY-2-PYRONES[1]

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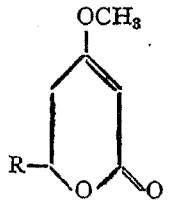
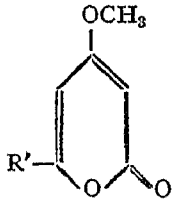
THE plant kawa kawa (*Piper methysticum*) has been used[2a, b] from ancient times to prepare a narcotic beverage by inhabitants of the South Pacific Islands. Its chemical examination, especially by Borsche and Co-workers,[3] has led to the isolation of several crystalline constituents which include kawain (I), dihydrokawain (II), methysticin (III), dihydromethysticin (IV) and yangonin (V). A pharmacological examination by Van Veen,[4] reported in 1939, indicated the active constituent to be II, referred to by him as marindinin. During the course of the present work, other reports[5–7] of pharmacological screening of the constituents of kawa kawa for central nervous system activity have appeared and these indicate that methysticin (III) and dihydromethysticin (IV) are the most active. The syntheses of all the constituents except II have been reported.[8–12]



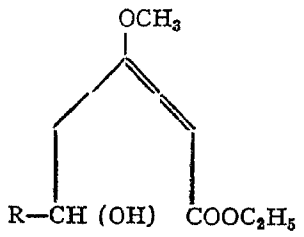
I, R = Styryl
II, R = β-Phenylethyl
III, R = 3, 4-Methylenedioxystyryl
IV, R = β-(3, 4-Methylenedioxyphenyl) ethyl
VII, R = Phenyl
VIII, R = 3, 4-Methylenedioxyphenyl
IX, R = *p*-Anisyl
X, R = α-Naphthyl



V, R' = *p*-anisyl
XI, R' = 3, 4-Methylenedioxyphenyl
XII, R' = Styryl or β-Pyridyl

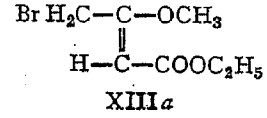
At the commencement of the present study the only published report on the pharmacological examination of kawa kawa was that of Van Veen[4] and it was of interest to prepare racemic marindinin for pharmacological

evaluation in view of the reported activity of the naturally occurring dextro form. *dl*-Kawain was prepared by the method of Kostermans[9] involving the Reformatsky reaction of cinnamaldehyde with ethyl-γ-bromo-β-methoxy crotonate. The use of zinc in the form of dust and longer periods of reaction furnished an improved yield (33·5%). Catalytic reduction of *dl*-kawain with palladised charcoal afforded *dl*-marindinin in 57·5% yield. Prolonged periods of hydrogenation gave acidic products probably resulting from the cleavage of the pyrone ring. The Reformatsky reaction of hydro-cinnamaldehyde directly with ethyl-γ-bromo-β-methoxy-crotonate was also studied. The reaction mixture, when worked up, yielded an oil which when chromatographed on alumina furnished *dl*-marindinin but only in 8·6% yield. This poor yield is probably due to the greater tendency of the intermediate VI *a* as compared to VI *b* to lose water than to cyclise by loss of ethanol. *dl*-Marindinin is a colourless crystalline compound m.p. 72–73° and is virtually identical in infra-red and ultraviolet absorptions with a sample of *d*-marindinin (reported m.p. of the latter 56–58°[3b], 60°[4]).

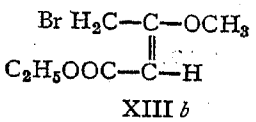


VI *a*, R = β-Phenylethyl
VI *b*, R = Styryl

It was then considered of interest to prepare some analogues of marindinin and the synthesis of some 6-aryl-4-methoxy-5, 6-dihydro-2-pyrones was undertaken in the first instance. The Reformatsky reactions of benzaldehyde, piperonal, *p*-anisaldehyde and α-naphthaldehyde gave 6-phenyl (VII), 6-piperonyl (VIII), 6-*p*-anisyl (IX) and 6-α-naphthyl (X)-4-methoxy-5, 6-dihydro-2-pyrones respectively. The yields of the dihydropyrones ranged from 23–31% except in the case of 6-piperonyl derivative (VIII) which was obtained in 55% yield. The unsatisfactory yields of 5, 6-dihydropyrones in such Reformatsky reactions may be due to the fact that ethyl γ-bromo-β-methoxy-crotonate employed by us and also by previous workers[9, 12, 13] is a mixture of the geometric form XIII *a* with the form XIII *b*. Only the latter can give rise to a Reformatsky product capable of undergoing cyclisation.



XIII *a*



XIII *b*

The availability of 6-substituted-5, 6-dihydro-4-methoxy-2-pyrones presents an attractive approach to the synthesis of the naturally occurring pyrone 4-methoxy paracotoin[14, 15] (XI), not hitherto synthesised and also to other similar pyrones (XII).[14, 15] Studies on the dehydrogenation of the 5, 6-dihydro-4-methoxy-2-pyrones as well as the synthesis of other types of analogues of marindinin are in progress.

Experimental

Ethyl-γ-Bromo-β-Methoxy-crotonate (XIII)

Ethyl-β-methoxy-crotonate was prepared and brominated essentially according to the method of Kostermans[9] to give XIII. For large-scale preparations of ethyl β-methoxy-crotonate, the following method based on that of Michael[16] and not involving large amounts of diazomethane was preferred.

To a well-cooled mixture of ethyl acetoacetate (80 g.) and methyl ortho-formate (70 g.) was added concentrated sulphuric acid (1·5 ml.). The mixture was kept in an ice-chest for 24 hours and then at room temperature for an additional 24 hours. Excess anhydrous potassium carbonate was added, the mixture filtered and freed of unreacted methyl ortho-formate *in vacuo*. The residue was taken up in ether (200 ml.) and washed three times with 2 N sodium hydroxide solution (75 ml.) and then with water. After drying, the ether was removed and the residue distilled. The fraction, b.p. 178–96°, was collected and refractionated to give 25 g. of material, b.p. 186–92°.

General Procedure

6-Aryl-5, 6-Dihydro-4-Methoxy-2-Pyrones

A mixture of 0·05 mole of the freshly distilled aldehyde, 0·05 mole of ethyl γ-bromo-β-methoxy-crotonate and 0·05 g.at. of purified zinc dust in 80 ml. of dry benzene was taken in a 250 ml. 3-necked flask fitted with a condenser and mercury sealed stirrer. The reaction was initiated by warming the mixture gently on the water-bath and, if necessary, by adding a pinch of iodine. After allowing the initial reaction to subside, the mixture was refluxed on the water-bath for 3½ hours. The brown reaction mixture was then cooled, decomposed with saturated ammonium chloride solution and the benzene layer separated. The aqueous layer was re-extracted with benzene and the combined layers were washed with water and dried over anhydrous magnesium sulphate. Removal of the solvent gave a residue which when diluted with 5–10 ml. of ether and allowed to stand in the ice-chest for a few hours, deposited yellow crystals. The crystals were collected and crystallised from ethanol to give the colourless products.

TABLE I

Lists the serveral pyrones thus prepared and some of their properties

Aldehyde	Product	M.P.	Yield (%)	Formula	Calculated		Found		I.R. Absorptions $\lambda_{max.}^{CHCl_3, \mu}$	U.V. Absorptions $\lambda_{max.}^{EtoH}$ $m\mu$ ($\log_{10}\epsilon$)
					% C	% H	%C	% H		
Cinnamaldehyde	I	145–46°	33·5	$C_{14}H_{14}O_3$	73·0	6·1	73·2	6·3	5·86, 6·13	244 (4·44), 281 (3·19), 291 (3·04)
Hydrocinnamaldehyde ..	II*	72–73°	8·6	$C_{14}H_{16}O_3$	72·4	7·0	72·3	7·1	5·87, 6·13	234 (4·08)
Benzaldehyde ..	VII[17, 18]	143–44°	31·0	$C_{12}H_{12}O_3$	70·6	5·9	70·5	5·7	5·87, 6·18	235 (4·08)
Piperonal ..	VIII	158–59°	54·5	$C_{13}H_{12}O_5$	62·9	4·8	62·7	4·8	5·87, 6·18	238 (4·09)
p-Anisaldehyde ..	IX	95–96°	31·0	$C_{13}H_{14}O_4$	66·7	6·0	66·9	5·9	5·87, 6·18	229 (4·26)
α-Naphthaldehyde	X	154–55°	26·0	$C_{16}H_{14}O_3$	75·6	5·5	75·1	5·7	5·83, 6·12	282 (4·01)

* The crude Reformatsky product was chromatographed as described elsewhere in the experimental section.

dl-*Marindinin* (dl-*Dihydrokawain*) (*II*)

(*a*) *From Hydrocinnamaldehyde.*—The crude Reformatsky product from this aldehyde was a liquid which was chromatographed over alumina. Elution with a 7 : 3 mixture of ether-petroleum ether (b.p. 60–80°) furnished product m.p. 68–70° C. Two crystallisations from ether yielded pure *dl*-marindinin, m.p. 72–73°, yield 8·6%.

(*b*) *By Reduction of Kawain* (*I*).—A suspension of 1 g. of *dl*-kawain in 50 ml. of methanol was hydrogenated over 30% palladium on charcoal at 50 p.s.i. for 12 minutes. The catalyst was filtered off and the filtrate freed of solvent. The residual liquid was taken up in ether and acidic impurities removed by washing the ether solution with 5% sodium bicarbonate solution. Removal of ether afforded a liquid which solidified when cooled. Two crystallisations from ether yielded 0·58 g. (57·5%) of colourless crystals m.p. 72–73° undepressed by and having identical U.V. and I.R. absorptions with product obtained in (*a*).

Summary

Some 6-substituted-5, 6-dihydro-4-methoxy-2-pyrones including the racemic form of marindinin, reported to be an active sedative principle of piper methysticum are described.

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