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The Synthesis of Flemichapparin-A and Its Derivatives

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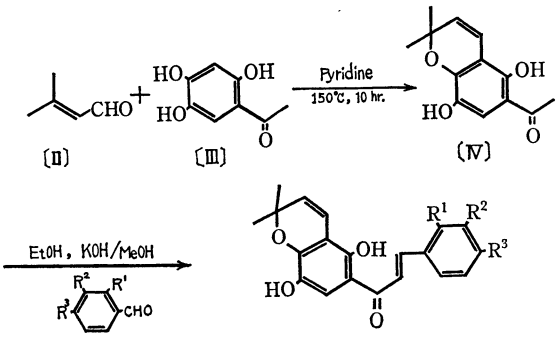
Synopsis. Some chromenochalcones including Flemichapparin-A were synthesized in 53—63% yields from 6-acetyl-5,8-dihydroxy-2,2-dimethylchlomene and benzaldehydes.

Some chromenochalcones are naturally occurring compounds[1] and are expected to have some biological activities. Recently some papers on the synthesis of these compounds have appeared.[2]

The present authors have studied the synthesis of chromenochalcones, especially those which contain the isoprene skeleton in part.[3] These compounds contained Flemichapparin-A which was recently isolated from *Flemingia Chappar* Ham (Leguminosae). In this paper, we wish to report on these studies.

6-Acetyl-5,8-dihydroxy-2,2-dimethylchromene [IV] was obtained by the reaction of 2,4,5-trihydroxyacetophenone [III] with β-methylcrotonaldehyde [II] in pyridine.

The Claisen-Schmidt condensation of IV with various benzaldehydes (benzaldehyde, 2,4-dimethoxybenzaldehyde, 3,4-dimethoxybenzaldehyde and 4-methoxybenzaldehyde) gave chromenochalcones in 53—63% yields. Among these compounds, the data of I agreed with those of Flemichapparin-A.[1-c,2-d]

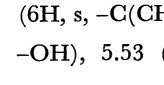
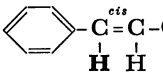


(II) (III) (IV)

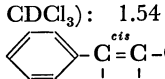
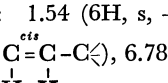
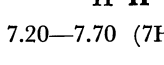
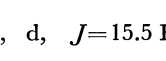
	R^1	R^2	R^3
[I]	H	H	H
[V]	OCH_3	H	OCH_3
[VI]	H	OCH_3	OCH_3
[VII]	H	H	OCH_3

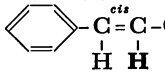
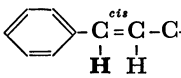
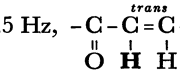
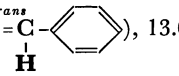
Experimental

6-Acetyl-5,8-dihydroxy-2,2-dimethylchromene [IV]. β-Methylcrotonaldehyde (II, bp 39—40 °C/15 mmHg, 8.4 g, 0.1 mol) and 2,4,5-trihydroxyacetophenone (III, mp 198—200 °C, 8.4 g, 0.05 mol) were dissolved in pyridine (4.0 g, 0.05 mol) and were then heated with stirring at 150 °C for 10 hr. The reaction mixture was evaporated, and the residue was chromatographed on silica-gel. The fraction eluted by benzene afforded 6-acetyl-5,8-dihydroxy-2,2-dimethylchromene (IV, 58% yield) as yellow needles.

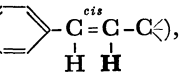
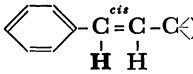
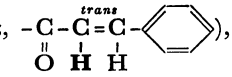
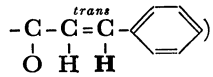
Mp 153—154 °C (recryst. from petroleum ether); IR (cm^{-1}, KBr disk): 3400 (-OH), 1640 (C=O), 1250 (-C-O-C-), 870 (penta substn. benzene); PMR (δ, $CDCl_3$): 1.50 (6H, s, $-C(CH_3)_2$), 2.49 (3H, s, $-COCH_3$), 5.28 (1H, broad s, -OH), 5.53 (1H, d, J=10.0 Hz, ), 6.70 (1H, d, J=10.0 Hz, ), 7.09 (1H, s, aromatic H), 12.60 (1H, s, -OH). Found C, 66.77; H, 6.03%. Calcd for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02%.

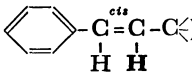
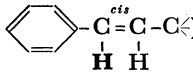
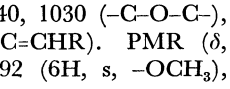
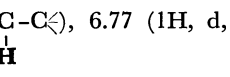
Chromenochalcones. A solution of IV (234 mg, 0.001 mol) and benzaldehydes (0.001 mol) in ethanol (4 ml) was added, under cooling under nitrogen, to 2 g of KOH in methanol (4 ml). After the reaction mixture had then stood at room temperature for 3—5 days, dilution, acidification (with 5 ml of 0.1 M-HCl), extraction with ether, and chromatography on silica-gel eluted by *n*-hexane–AcOEt (95 : 5 v/v) afforded chromenochalcones, which were identified by means of IR, PMR, and elemental analysis.

2′,5′-Dihydroxy-3′,4′(5″,6″)2″,2″-dimethyl-α-pyranochalcone (I). Yield, 53%; mp 190—192 °C (orange plates). IR (cm^{-1}, KBr disk): 3400 (-OH), 1640 (C=O), 1240 (-C-O-C-), 970 (*trans* RHC=CHR), 760 (*cis* RHC=CHR). PMR (δ, $CDCl_3$): 1.54 (6H, s, $-C(CH_3)_2$), 5.60 (1H, d, J=10.0 Hz, ), 6.78(1H, d, 10.0 Hz, ), 7.20—7.70 (7H, m), 7.48 (1H, d, J=15.5 Hz, ), 7.90 (1H, d, J=15.5 Hz, ), 13.37 (1H, s, -OH). Found C, 74.18; H, 5.86%. Calcd for $C_{20}H_{18}O_4$: C, 74.52; H, 5.63%. The mp and PMR data agreed with that on Flemichapparin-A in the literature.[1-c] (lit,[1-c] mp 191—192 °C; PMR (δ, $CDCl_3$); 1.50, 5.58, 6.76, 7.20—8.00, 13.60).

2′,5′-Dihydroxy-2,4-dimethoxy-3′,4′(5″,6″)2″,2″-dimethyl-α-pyranochalcone (V). Yield, 63%, mp 214—215 °C (yellow plates). IR (cm^{-1}, KBr disk): 3400 (-OH), 1640 (C=O), 1365 ($-OCH_3$), 1235, 1030 (-C-O-C-), 930 (*trans* RHC=CHR), 730 (*cis* RHC=CHR). PMR (δ, $CDCl_3$): 1.50 (6H, s, $-C(CH_3)_2$), 3.86 (6H, s, $-OCH_3$), 5.58 (1H, d, J=10.0 Hz, ), 6.45 (1H, s, -OH), 6.77 (1H, d, J=10.0 Hz, ), 6.50—7.50 (4H, m), 7.50(1H, d, J=15.5 Hz, ), 8.12 (1H, d, J=15.5 Hz, ), 13.60 (1H, s, -OH). Found C, 69.08; H, 5.68%. Calcd for $C_{22}H_{22}O_6$: C, 69.10; H, 5.80%.

2′,5′-Dihydroxy-3,4-dimethoxy-3′,4′(5″,6″)2″,2″-dimethyl-α-

pyranochalcone (VI). Yield, 54%, mp 192—193 °C (orange plates). IR (cm^{-1}, KBr disk): 3400 (–OH), 1640 (C=O), 1360, 1170 ($-OCH_3$), 1240, 1030 (–C–O–C–), 930 (*trans* RHC=CHR), 730 (*cis* RHC=CHR). PMR (δ, $CDCl_3$): 1.50 (6H, s, $-C(CH_3)_2$), 3.92 (6H, s, $-OCH_3$), 5.58 (1H, d, J=10.0 Hz, ), 6.77 (1H, d, J=10.0 Hz, ), 6.95 (1H, s, –OH), 7.10—8.00 (4H, m), 7.25 (1H, d, J=15.5 Hz, ), 7.60 (1H, d, J=15.5 Hz, ), 13.47 (1H,s, –OH). Found C, 69.07; H, 5.78%. Calcd for $C_{22}H_{22}O_6$: C, 69.10; H, 5.80%.

2′,5′-Dihydroxy-4-methoxy-3′,4′(5″,6″)2″,2″-dimethyl-α-pyranochalcone (VII). Yield, 59%; mp 196—197 °C (orange plates). IR (cm^{-1}, KBr disk): 3400 (–OH), 1640 (C=O), 1360, 1170 ($-OCH_3$), 1240, 1030 (–C–O–C–), 930 (*trans* RHC=CHR), 730 (*cis* RHC=CHR). PMR (δ, $CDCl_3$): 1.50 (6H, s, $-C(CH_3)_2$), 3.92 (3H, s, $-OCH_3$), 5.60 (1H, d, J=10.0 Hz, ), 6.79 (1H, d, J=10.0 Hz, ), 7.00 (1H, s, –OH), 7.10—7.70 (5H, m), 7.60 (1H, d, J=15.5 Hz, ), 8.20 (1H, d, J=15.5 Hz, ), 13.48 (1H, s, –OH). Found C, 71.59; H, 5.84%. Calcd for $C_{21}H_{20}O_5$: C, 71.58; H, 5.72%.

References

1) a) B. S. Bajawa, P. L. Khanna, and T. R. Seshadri, *Curr. Sci.*, **41**, 814 (1972). b) G. Cardillo, L. Merlini, and R. Mondelli, *Tetrahedron*, **24**, 497 (1968). c) G. Cardillo, A. Gennaro, L. Merlini, G. Nasini, and S. Servi, *Tetrahedron Lett.*, **1970**, 4367. d) S. K. Mukerjee, P. Sharma, and T. R. Seshadri, *Indian J. Chem.*, **10**, 585 (1972).

2) a) G. Cardillo and L. Merlini, *Tetrahedron*, **24**, 4825 (1968). b) W. M. Bandaranayake, L. Crombie, and T. R. Whiting, *Chem. Commum.*, **1969**, 58. c) S. K. Mukerjee, P. Sharma, and T. R. Seshadri, *Indian J. Chem.*, **11**, 985 (1973). d) N. Adityachaudhury, D. Ghosh, A. Chaudhury, and C. L. Kirtania, *J. Indian Chem. Soc.*, **50**, 363 (1973).

3) a) Presented at 26th Annual Meeting of the Chemical Society of Japan, Tokyo, April, 1972, Preprint Vol. III, p. 1639 (1972). b) Presented at the Meeting of the Chemical Society of Japan (Tokai branch), Preprint, p. 191 (1973).