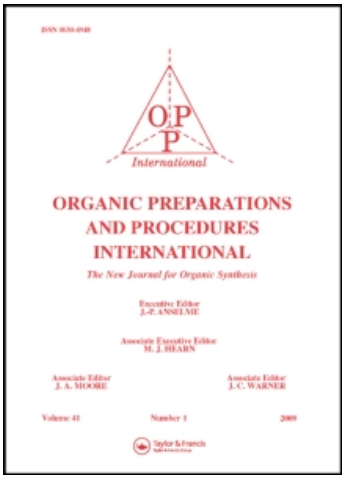

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A CONVENIENT METHOD FOR THE PREPARATION OF 6-CARBOXYMETHYLFLAVONE

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A CONVENIENT METHOD FOR THE PREPARATION OF 6-CARBOXYMETHYLFLAVONE

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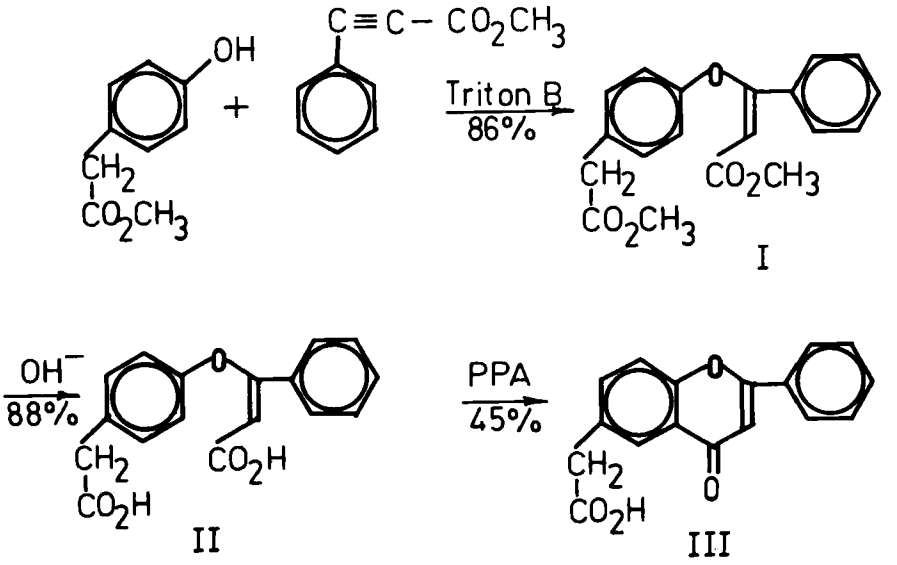
The choleretic and anti-inflammatory activities of 6-carboxymethylflavone (III) have been recently claimed in several patents.[1] It was originally prepared[2] in an overall yield of 11% from 2-hydroxy-5-methylacetophenone by a six-step synthesis. In connection with synthetic work on anti-inflammatory agents, a larger quantity of this valuable intermediate was required.



We now report a convenient three-step synthesis of the title compound (III) in better yields from methyl p-hydroxyphenyl acetate and methyl phenylpropiolate, a modification of Ruhemann's[3] method. The intermediates diester (I) and the diacid (II) are reported for the first time.

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were measured with a Perkin-Elmer 237 Grating Spectrometer. The NMR spectra were recorded on a Varian A-90 instrument with TMS as internal reference and chemical shifts are expressed in δ values. Elemental analyses were carried out using Hosli Micro-Combustion apparatus MK 101.

Methyl-β-(4-methoxycarbonylmethylphenyloxy)-β-phenylacrylate (I).- A mixture of methyl p-hydroxyphenylacetate (16.6 g, 0.1 mole), methyl phenylpropiolate (16 g, 0.1 mole) and Triton B (5 ml) was heated at 150-160° in an oil bath for 2 hrs. The cooled reaction mixture was poured into cold water (500 ml) and extracted with ether (4 x 75 ml). The ethereal extract was washed with 3% cold aqueous sodium hydroxide followed by dil. HCl and finally with water. The ethereal layer was dried over anhydrous sodium sulphate. Removal of ether left a viscous pale yellow oil, which was distilled in vacuo giving 28 g (86%) of pure I, bp. 225-230° (0.1 mm). IR (film): 1625 (C=C) and 1725 cm^{-1} (ester C=O); NMR (CCl_4): δ 3.15-3.55 (8H, m), 5.15 & 6.0 (1H, 2s), 6.6-7.65 (9H, m).

Anal. Calcd. for $C_{19}H_{18}O_5$: C, 69.93; H, 5.52

Found: C, 70.00; H, 5.28

β-(4-Carboxymethylphenyloxy)-β-phenylacrylic acid (II).- A mixture of I (10 g) in methanol (150 ml) and 10% aqueous sodium hydroxide solution (150 ml) was heated to reflux for 1 hr. in a water bath and left overnight at room temperature. The reaction mixture was washed with ether to remove the unreacted diester. The aqueous layer was acidified with dil. HCl at 0-5° and thoroughly extracted with ether. The ethereal layer was extracted with 5% sodium bicarbonate solution and the bicarbonate layer was neutralized with dil. HCl. The resulting product was re-extracted with ether (4 x 75 ml), washed with water and dried over anhydrous sodium sulphate. Removal of ether gave a pale yellow solid which was recrystallized from ethyl acetate to give 8.0 g (88%) of pure II, mp. 170-175°. IR (nujol): 1625 (C=C) and 1690 cm^{-1} (-COOH).

Anal. Calcd. for $C_{17}H_{14}O_5$: C, 68.39; H, 4.698.

Found: C, 68.28; H, 5.16.

6-Carboxymethylflavone (III).- The diacid II (6 g, 0.02 mole) was taken in polyphosphoric acid (150 g) and heated with stirring at 90° for 4 hrs. The reaction mixture was poured into cold water (1.25 lit.) and extracted thoroughly with ether (4 x 250 ml). The ethereal extract was washed with water and dried over anhydrous sodium sulphate. Removal of ether gave a pale brown solid which was recrystallized from acetic acid to give 2.5 g (45%) of pure III, mp. 223-225°, identical (mmp and IR) with authentic sample prepared by literature method.[2] IR (nujol): 1650 (pyrone C=O) and 1690 cm^{-1} (-COOH); NMR (TFA): δ 4.25 (2H, s, CH_2), 7.7 (2H, d, J = 9 Hz, 2'-H and 6'-H), 7.9 (1H, s, 3-H), 8.1-8.45 (5H, m, 3',4',5', 7 and 8-H),

8.55 (1H, s, 5-H).

Anal. Calcd. for $C_{17}H_{12}O_4$: C, 72.83; H, 4.28.
Found: C, 72.68; H, 4.517.

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