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SYNTHESIS OF PRATENSEIN, 5,7,3'-TRIHYDROXY-4'-METHOXYISOFLAVONE

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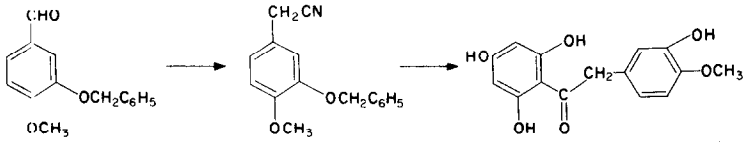
Previous work[1] in this laboratory on the oestrogenic constituents of red clover (Trifolium pratense) has resulted in the isolation of a new isoflavone, $C_{16}H_{12}O_6$, for which the name pratensein was proposed. On the basis of micro-degrative and paper chromatographic evidence its constitution was assigned as 5,7,3'-trihydroxy-4'-methoxyisoflavone (IV,R=H)[2]. In view of the very small amount of material available (ca 40 mg. from 36 kg. of fresh clover) it was felt most desirable to synthesize the substance, both to confirm the structure and to make it accessible for pharmacological study.

Pratensein has now been synthesised from the deoxybenzoin (III) by ring cyclisation with ethoxalyl chloride, following the general method for polyhdroxyisoflavones due to Baker and Ollis[3].

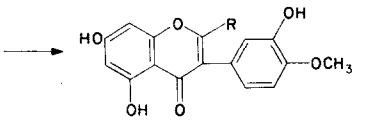
[1] E. Wong, J. Sci. Food Agric. 13, 304 (1962).

[2] E. Wong, Chem. & Ind. (London), 1963 (1961).

[3] W. Baker and W. D. Ollis, Nature 169, 706 (1952); W. Baker, J. Chadderton, J. B. Harborne, and W. D. Ollis, J. Chem. Soc. 1852 (1953).



(I) (II) (III)



(IV)

O-Benzylisovanillin (I) was converted to the corresponding substituted phenylacetonitrile (II) by the following transformations. Reaction of (I) with rhodanine[4] yielded a yellow condensation product (m.p. 221-6°) which was cleaved with alkali to the corresponding thioketo acid (m.p. 155-6°). This on reaction with hydroxylamine yielded the oximino acid (m.p. 156°. Found: C,64.28; H,5.40; N,4.88. $C_{17}H_{17}O_5N$ requires: C,64.91; H,5.44; N,4.46%). Treatment of the oximino acid with acetic anhydride effected decarboxylation and dehydration to the nitrile (II) (m.p. 80°. Found: C,76.21; H,6.28; O,12.80. $C_{16}H_{15}O_2N$ requires: C,75.86; H,5.97; O,12.64%) in an over-all yield of ca 30%.

Hoesch condensation of phloroglucinol and 3-benzyloxy-4-methoxyphenylacetonitrile (II) yielded the deoxybenzoin (III) (m.p. 105°, resolidifying, and 196-9°. Tetra-acetate m.p. 168-70°.

[4] P. L. Julian and B. M. Sturgis, J. Am. Chem. Soc. 57, 1126 (1935).

Found: C,60.38; H,5.08; OCH_3,6.27; CH_3CO,38.11. $C_{23}H_{22}O_{10}$ requires: C,60.24; H,4.84; OCH_3,6.77; CH_3CO,37.56%) debenzylation having taken place under the acid condition of the reaction. The deoxybenzoin (III) was treated with ethoxalyl chloride in pyridine and the total ethoxalyation product was hydrolysed with sodium carbonate in aqueous ethanol to yield the isoflavone carboxylic acid (IV, R = COOH m.p. 273-5° with effervescence). Thermal decarboxylation of the acid gave a dark gum from which pratensein (IV, R = H) was isolated by sublimation and recrystallisation from ethanol (m.p. 271-3°. Found: C,63.40; H,4.18; OCH_3,10.40. $C_{16}H_{12}O_6$ requires: C,64.00, H,4.03; OCH_3,10.33%).

The synthetic isoflavone was identical with the natural product with respect to m.p., infrared spectrum, m.p. of triacetate derivative and chromatographic behaviour, thus confirming the structure (IV, R = H) for pratensein.

Preliminary results indicate that pratensein is oestrogenic in mice at a dose of 12 mg. per mouse, as tested by the uterine weight method[5].

A detailed description of the isolation, structural determination and synthesis of pratensein will be published shortly.

[5] E. Wong, D. S. Flux and G. F. Wilson, unpublished results.