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# THE SYNTHESIS OF 1-HYDROXY-7-METHOXY-4-ISOPROPYL-1,6-DIMETHYL -2(1H)-NAPHTHALENONE — A CYTOKINETIC COMPOUND FROM COTTON

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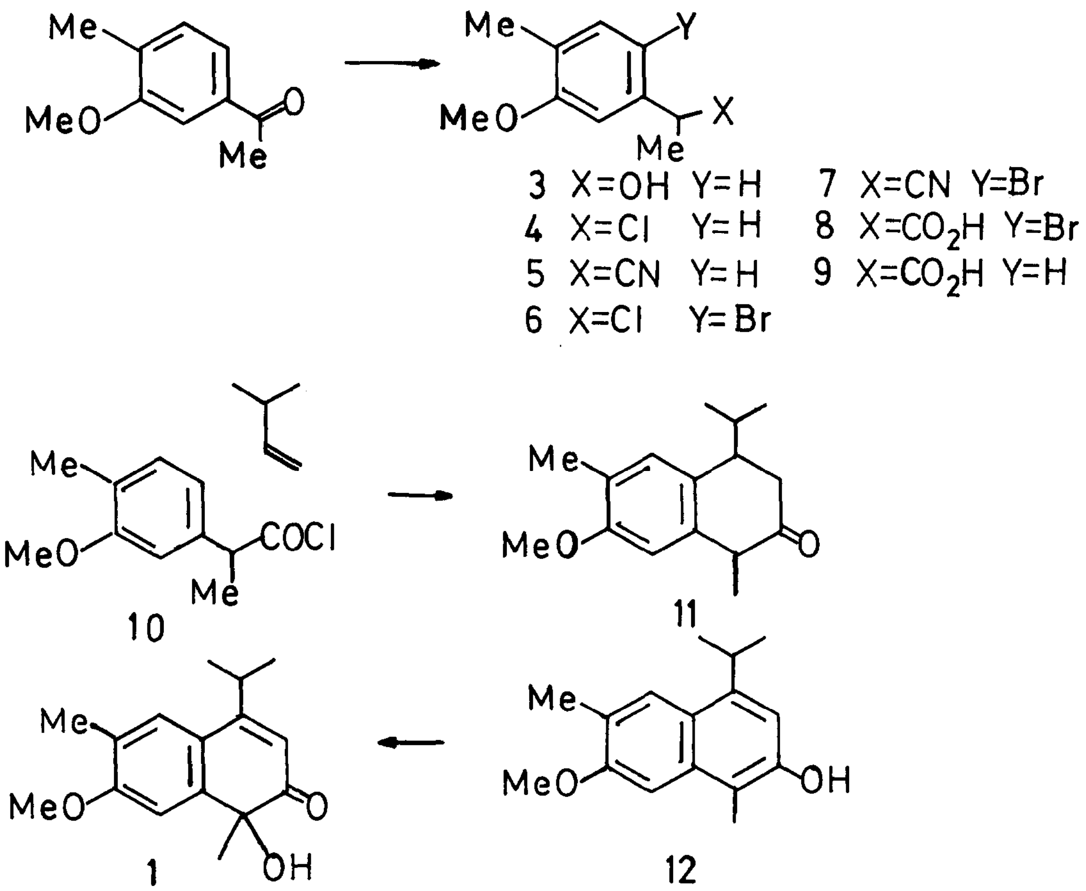
The isolation of 1-hydroxy-7-methoxy-4-isopropyl-1,6-dimethyl-2(1H)-naphthalenone (1) from cotton has been described recently.[1] Interest in this compound stems from the report of its in vitro chemotactic activity towards polymorphonuclear leukocytes[2] and its possible implication in the onset of byssinosis, a clinical syndrome which is associated with workers inhaling cotton dust.[3] We report here a simple synthesis of compound 1.

Reaction of 3-methoxy-4-methylbenzoic acid with lithium hydride and dimethoxyethane followed by the addition of methyl lithium gave the methyl ketone 2[4] (99%). Reduction of 2 with sodium borohydride in isopropanol afforded the alcohol 3 which was converted to the corresponding chloride 4 upon treatment with thionyl chloride in benzene.

Attempts to convert 4 to the nitrile 5 using potasium cyanide in a variety of solvents and under many different reaction conditions, including photochemical activation,[5] led to poor yields of the desired product; in most cases if reaction occurred the alcohol 2 appeared as the major component. In contrast to the difficulty experienced with this reaction, the analogous conversion of 6 to 7[6] with potassium cyanide proceeded in 91% yield under mild conditions (DMF, 25° 48hr). The role which the 6-bromo substituent plays in facilitating the displacement of chloride by cyanide at the expense of formation of the alcohol is not clear, and this finding is under further study. Hydrolysis of the nitrile 7 to the carboxylic acid 8 (refluxing 6N KOH containing 10% $H_2O_2$) and subsequent reductive debromination by catalytic hydrogenation in 1N KOH gave 9 (90%). The carboxylic acid 9 was converted to the acid chloride 10 with thionyl chloride in refluxing benzene and after spectral characterization, it was reacted immediately with 3-methyl-1-butene and aluminum chloride in $CH_2Cl_2$ (1 hr at -70°, 24 hr at 0°) to afford the tetralone 11 (69%). This latter reaction represents a useful extension of related reactions which have been previously used for the synthesis of benzocyloalkanones.[7]

Dehydrogenation of 11 (30% Pd-C in refluxing decalin) afforded an unstable phenol 12, mp 116-7°(55%), which was characterized spectrally and by conversion to its stable 3,5-dinitrobenzoate, mp 218°. Oxidation of 12 with diphenyl selenic anhydride[8] (refluxing $CH_2Cl_2$, 3hr) gave the naphthalenone 1 (85%).

The synthetic material showed the same cellular activity as the natural material, which appears to be cytokinetic[9] rather than chemotactic towards leukocytes.



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