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SYNTHESIS OF UVARETIN, AN ANTITUMOUR AND ANTIMICROBIAL FLAVONOID

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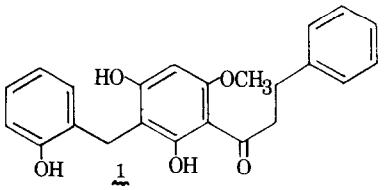
Abstract: The flavonoid uvaretin (1-(2,4-dihydroxy-6-methoxy-3-((2-hydroxyphenyl)-methyl)-phenyl)-3-phenyl-1-propanone), known to be active against some tumours and several bacteria, has been synthesized in six steps from 2',4',6'-trimethoxyacetophenone, 2-hydroxybenzaldehyde and benzaldehyde.

A number of flavonoids with a 2-hydroxybenzyl side chain has been isolated from the bark and roots of several species of Uvaria, a genus of tropical African plants (1-3). Uvaretin (1) is the major one of these flavonoids.



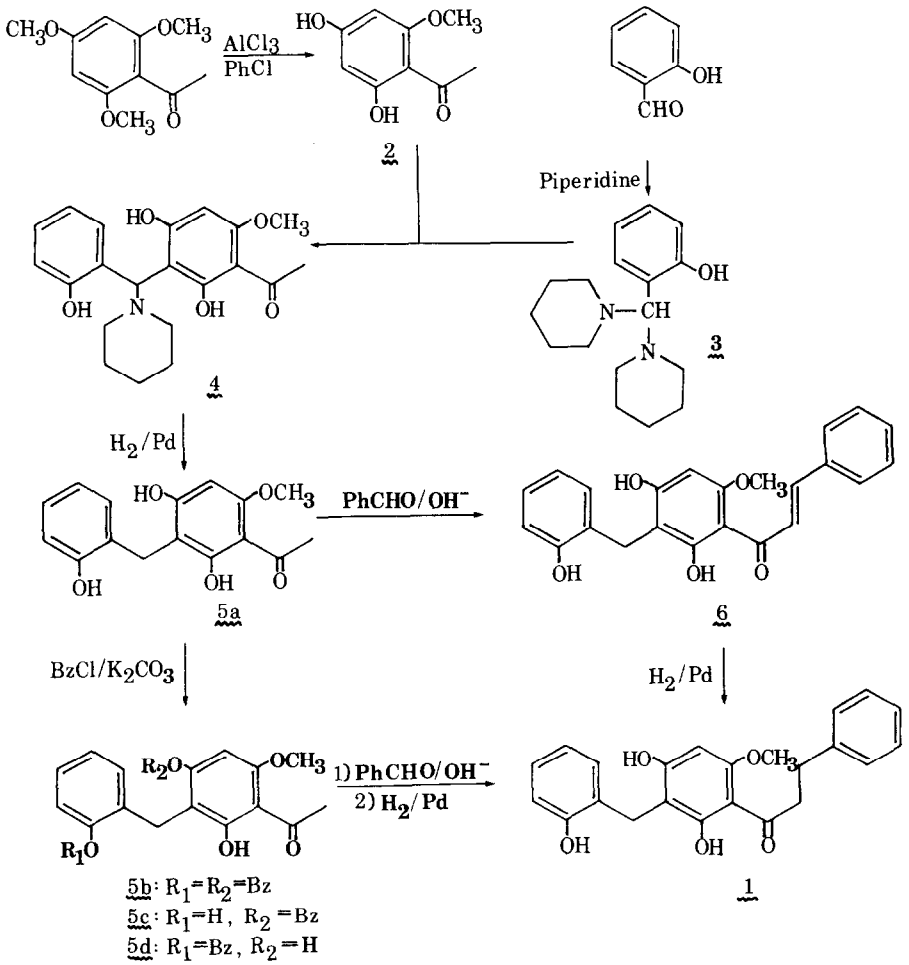
1

It has been shown (1,2,4) that 1, as well as the minor 2-hydroxybenzylated flavonoids, inhibits the growth of P-388 lymphocytic leukemia in mice in vivo and human nasopharynx carcinoma cells in vitro. In addition, 1 inhibits the bacteria Staphylococcus aureus, Bacillus subtilis and Mycobacterium smegmatis (4,5). A synthesis of 1 would seem useful in view of its interesting biological properties.

To our knowledge, no such synthesis has been published until now. In this communication, we describe a synthesis of uvaretin, in which the key step

is a C-benzylation of 2´,4´-dihydroxy-6´-methoxyacetophenone by the aminal method recently described by Kallay and co-workers (6,7). This method for alkylation and aralkylation of m-dihydroxybenzene derivatives, although reported to be a versatile and effective one, has not found much use yet.

Substance 2, 2´,4´-dihydroxy-6´-methoxy-acetophenone, was synthesized by demethylation of 2´,4´,6´-trimethoxyacetophenone with $AlCl_3$ in chlorobenzene (8). A mixture of 2´-hydroxy-4´,6´-dimethoxy-, 2´,6´-dihydroxy-4´-methoxy-, 2´,4´-dihydroxy-6´-methoxy- and 2´,4´,6´-trihydroxyacetophenone was obtained, from which 2 was purified by preparative TLC (yield 29 %). When nitrobenzene was used as solvent instead, only the dimethoxy derivative was obtained.



Substance 2 was condensed with 2-hydroxyphenyl-bis-1,1-piperidinomethane, 3 (synthesized from 2-hydroxybenzaldehyde and piperidine (9)) by boiling for 4 hrs in ethanol, furnishing 2´,4´-dihydroxy-3´-((2-hydroxyphenyl)-(1-piperidino)-methyl)-6´-methoxyacetophenone, 4, in a 60 % yield. Attempted condensation of 4 with benzaldehyde was fruitless. For that reason, the piperidine moiety of 4 was removed by catalytical hydrogenation, using 10 % Pd/C as catalyst. This yielded 2´,4´-dihydroxy-3´-(2-hydroxybenzyl)-6´-methoxyacetophenone, 5a. It was found that, due to the formation of another, less polar, substance which has not been identified as yet, the highest yields (50-60 %) were obtained by terminating the reaction while some starting material was still present.

Attempted aldol condensation of 5a with benzaldehyde, using an acid catalyst, resulted in recovery of the starting substances. When condensation was carried out with 50 % aqueous KOH as catalyst, a 9 % yield of 2´,4´-dihydroxy-3´-(2-hydroxybenzyl)-6´-methoxychalcone, 6, was obtained after a reaction time of 15 days at 4^{o} in an N_2 atmosphere. Hydrogenation of 6 (catalyst as above) then gave 1 in a 75 % yield, identified by its mp (162-164^{o}, lit. (2) 164-165^{o}), and identical spectra (UV, IR, NMR, MS) with lit. (1,2).

In an attempt to improve the yield of the aldol condensation, substance 5a was benzylated with $BzCl/K_2CO_3$ in acetone by refluxing for 6 hrs, then the solution was kept for 16 hrs at room temperature before work-up. This gave a mixture of the dibenzylated derivative 5b and a monobenzylated one (5c or 5d), yield 10 and 21 %, respectively. It would seem possible that with a longer reaction time or a stronger benzylating agent, such as benzyl bromide, better yields might be obtained.

Aldol condensation of the benzyl ethers with benzaldehyde under the conditions described above yielded the corresponding chalcones in yields of 69 % (from 5b) and 79 % (from 5c/d). Catalytic hydrogenation finally resulted in de-O-benzylation as well as reduction of the double bond, giving 1, yield 74 % and 73 %, respectively. Thus, protecting the hydroxyl groups of 5a by benzylation more than tripled the total yield of 1.

In our opinion, this synthesis shows that the Kallay aminal reaction (6,7) is a useful one in C-alkylation and C-aralkylation of phenols, giving good yields under mild reaction conditions. Since a resorcinol or phloroglucinol structure is required, the reaction most probably occurs via a ketonic, non-aromatic equilibrium form of the substrate.

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REFERENCES

1. Cole,J.R., Torrance,S.J., Wiedhopf,R.M., Arora,S.K. and Bates,R.B.: J.Org. Chem. 41 (1976) 1852.
2. Lasswell,W.L. and Hufford,C.D.: J.Org.Chem. 42 (1977) 1295.
3. Hufford,C.D. and Oguntimein,B.O.: Phytochemistry 19 (1980) 2036.
4. Lasswell,W.L.: Ph.D. Thesis, University of Mississippi, 1977 (Diss. Abs. Int. B38 (1977) 1148).
5. Hufford,C.D. and Lasswell,W.L.: Lloydia 41 (1978) 151.
6. Kallay,F., Janzso,G., Egyed,I. and Baitz-Gacs,E.: Selective nuclear alkylation and aralkylation in the synthesis of flavonoids. In Farkas,L., Gabor,M. and Kallay,F.(ed.): Flavonoids and bioflavonoids. Elsevier,Amsterdam 1977.
7. Kallay,F., Janzso,G., Egyed,I. and Baitz-Gacs,E.: Acta Chim. Acad. Sci. Hung. 100 (1979) 311.
8. Gulati,K.C. and Venkataraman,K.: J.Chem. Soc. (1936) 267.
9. Knoevenagel,E. and Arnot,R.: Ber. Dtsch. Chem. Ges. 37 (1904) 4496.

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