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THE SYNTHESIS OF MYCOPHENOLIC ACID ANALOGUES THROUGH PRENYLATION OF 5,7-DIHYDROXYPHTHALIDES

L. Canonica, B. Rindone, and C. Scolastico

(Istituto di Chimica Organica dell'Università di Milano, V. Saldini 50, Milano, Italy)

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The biological properties of mycophenolic acid[1] prompted studies to provide analogues; some of them could be interesting as possible biosynthetic intermediates. Otherwise, the use of mycophenolic acid as a starting material for preparative purposes permits only a limited number of modifications[2], and its total synthesis, due to Birch[3], cannot be easily modified to yield its analogues.

This paper is concerned with a new synthesis of O-desmethylmycophenolic acid as well as some terpenoid side-chain modified compounds, using a 6-prenylation method of the 5,7-dihydroxyphthalides (1) and (2).

This prenylation was performed by treatment of a dioxane solution of the 5,7-dihydroxyphthalide (1 mole), at room temperature and in presence of Ag_2O (1.5 moles), with the proper allylic bromide (1.3 moles).

As reported also by other authors[3], the usual methods of prenylation of phenols[4] give negative results.

Table 1 indicates the reaction time, the meltig points and the yield of the compounds obtained with this method after purification of the resulting mixture by chromatography followed by crystallisation.

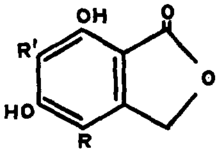
The confront of the N.M.R. values of the both benzylic and allylic protons in the compounds obtained by the two 5,7-dihydroxyphthalides (1) and (2) indicates that the side-chain is always introduced at C_6. Furthermore, compounds (4) and (7) are identical to those obtained by us by fermentation[5]. Compounds (4) and (5) were synthesised starting from the intermediate (8), whose preparation was performed by reaction of O-tritylgeraniol (9) with N-bromosuccinimide in aqueous t-butanol[6] to yield the bromohydrine (10). Treatment of (10) with K_2CO_3 in H_2O-CH_3OH yielded the epoxide (11). The subsequent treatment with $HClO_4$ in diglyme furnished the diol (12) which was cleaved with $NaIO_4$ in aqueous-tetrahydrofuran to give the tritylaldehyde (13), $C_{26}H_{26}O_2$, m.p. 90-92°. Tritylaldehyde (13) could be oxidised to the acid (14), $C_{26}H_{26}O_3$, m.p. 135-136°, by means of silver oxide in aqueous basic medium. Less satisfactory results were obtained by different oxidation procedures[7]. Hydrolysis of (14) in aqueous 80% acetic acid led to compound (15) which was methylated with diazomethane in ethyl ether to give (16). The bromide (8) was then obtained by allylic bromination with Ph_3P and CBr_4 in acetonitrile[8].

Satisfactory elemental analyses have been obtained for all new compounds.

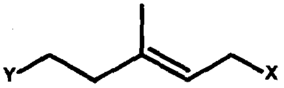
Table 1

Compound	m.p.	Reaction Time	Yield %
(3)	140–142°	120'	32
(4)(*)	193–194°	120'	36
(5)	107–110°	30'	36
(6)	98–100°	30'	34
(7)	88–90°	30'	28

(*) Condensation was performed with (8) and (1); (4) was obtained by hydrolysis of the corresponding methylester with aquoeus NaOH.



(1) R=H R'=H
(2) $R=CH_3$ R'=H
(3) R=H R'=Geranyl
(4) R=H $R'=HO_2C(CH_2)_2C(CH_3)=CHCH_2$
(5) $R=CH_3$ $R'=H_3CO_2C(CH_2)_2C(CH_3)=CHCH_2$
(6) $R=CH_3$ R'=Geranyl
(7) $R=CH_3$ R'=t,t-Farnesyl



(13) $X=OCPh_3$ Y=CHO
(14) $X=OCPh_3$ Y=COOH
(15) X=OH Y=COOH
(16) X=OH $Y=COOCH_3$
(8) X=Br $Y=COOCH_3$

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